NUTRITIONAL DIAGNOSIS

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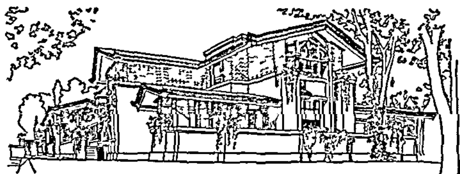
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NUTRITIONAL DIAGNOSIS

By

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to my good friend

Sue Cannon Price

FOREWORD

A PROGRAM of nutrition research was initiated by the author more than fifteen years ago in the Department of Medicine at Tulane University In its incipiency, research dealt largely with the B group of vitamins in human nutrition As the program expanded, investigation of *protein, carbohydrate, lipid, mineral and vitamin* metabolism has been included Basic biochemical research and studies in experimental animals as well as in man have been integral parts of the program A special clinic for nutritional diagnosis and therapy was established in the Hutchinson Memorial Clinic at Tulane and nutritional consultation services were initiated at Charity Hospital of Louisiana at New Orleans In addition, the program has included teaching of clinical and biochemical aspects of nutrition to undergraduate medical students and to post graduate students in both biochemistry and medicine Much of the material included in this review stems directly or indirectly from knowledge and experience gained through development of this nutrition program

The purpose of this monograph was to gather together and evaluate current information on nutritional diagnosis Need for a résumé in this field has been apparent for some time It is hoped that such a summary will prove useful to the practicing physician in evaluating the nutritional problems of his patients, that it will generate interest in the field of nutritional diagnosis and that it will stimulate investigation which may lead to more precise diagnosis in the future

Collection and choice of material for inclusion in this review has been a formidable task There are so many facets that it is difficult to cover the entire nutrition spectrum adequately in a reasonable amount of space In view of the extensive literature, it has not been possible to give individual credit to everyone who has made significant contributions, desirable as it would be to do so In the bibliography, reference has been made to reviews and symposia whenever possible, rather than to reports of individual research Findings which are generally accepted have not been annotated, while recent reports and new methods of diagnosis have received specific citation in most instances

Publication of this book provides a welcome opportunity to gratefully acknowledge the assistance of many persons, foundations and agencies Our nutrition program could not have reached its present status without the continued interest and financial support of the Nutrition Foundation, the Williams Waterman Fund of the Research Corporation and the Division of Research Grants and Fellowships of the Public Health Service

The author is most grateful for the assistance and cooperation of many distinguished colleagues The late Dr John Herr Musser, who was Professor of Medicine at Tulane University for many years stimulated my original interest in nutritional problems This interest was encouraged by Dr Russell Wilder under whom I was privileged to study at the Mayo Clinic The assistance and wise counsel of Dr C Glen King and Dr Robert R Williams over a number of years have been of inestimable value The opportunity of working with members of the Food and Nutrition Board of the National Research Council and of the Council on Foods and Nutrition of the

American Medical Association has been most stimulating and is deeply appreciated

I am indebted, also, to the past and present members of the Nutrition Research Group at Tulane University who have worked with me in the clinics, hospital wards and laboratories The help of my capable secretary is also gratefully acknowledged This book was written largely during summer vacations and I am indebted above all to my good friend Sue Cannon Price for her encouragement and understanding and for sharing the difficulties and frustrations inherent in preparation of this monograph

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NUTRITIONAL DIAGNOSIS

INTRODUCTION

NUTRITIONAL diagnosis is an integral part of every medical evaluation even when attention is directed primarily to some other phase of a patient's problem and nutritional therapy is an essential feature in the management of every disease state although it may involve only institution or maintenance of an adequate diet Unfortunately, the nutritional state of a patient is often taken for granted or dismissed with a cursory observation of the abundance or scarcity of bodily fat A note may be made in the record "well developed and well nourished" and investigation is pursued in other directions

In general, medical practice has not kept abreast of the tremendous advances in nutritional science and the refinements in nutritional diagnosis which have been evolved in recent years It is true that the health hazards of obesity are receiving considerable emphasis and the importance of electrolyte balance is recognized with increasing frequency Nevertheless, these are only facets, although important ones, in the broad field of nutrition Vitamins have been prescribed for a wide variety of major and minor complaints, often without reason or justifiable hope of efficacy Each new vitamin has been heralded as a panacea for many of the unsolved problems of medicine Such unscientific enthusiasm has resulted in unwarranted scepticism on the part of many physicians as to the importance of vitamins and of other nutritional factors as well, in the pathogenesis and therapy of disease

The term nutrition is often considered in a narrow

sense as meaning knowledge of the essential chemical substances which must be included in the diet and application of this knowledge to dietotherapy The science of nutrition embraces a much wider field Knowledge of the role of essential nutrients in metabolism, which includes the whole realm of nutritional biochemistry, is vital in the understanding of normal bodily function and the many disturbances which occur in disease Many types of disease, whether infectious, metabolic or degenerative, influence the nutritional state of the patient and in turn, nutrition influences the prevention, development and regression of many pathologic states

Nutritional diagnosis means much more than the detection of some overt deficiency disease, a concept prevalent some years ago Today, it is essential to think less in terms of specific deficiency states and more in terms of disturbances in the biochemical reactions of the body The diet must furnish the potential energy for basal metabolic processes and for physical activity and, also, all of the chemical substances needed for manufacture of new tissue Recent investigations, using isotopic techniques, have indicated that the components of cells are constantly being broken down and reconstituted, requiring continuous replenishment with essential nutrients (1) Nutritional diagnosis implies, therefore, evaluation of the biochemical milieu within and outside of the cells, as well as detection of abnormalities of function and structure of the organs and tissues of the body Recent studies of the role of mitochondria and other cellular units in oxidative metabolism link cytology and biochemistry closely together and may lead to better correlation between pathologic anatomical changes and biochemical abnormalities of body tissues and fluids

In general, nutritional deficiency occurs gradually al-

though the speed of development varies widely The reserve stores of nutrients are depleted before biochemical or physiological dysfunction develops Gross structural changes in tissues are usually late manifestations of severe or prolonged depletion

Attainment and maintenance of adequate nutrition is not difficult in the United States, since a wide variety of food is readily available Consequently, the importance of nutrition may not be appreciated sufficiently in this country, except in situations of extreme poverty and neglect or in severe illness In many countries of the world, serious degrees of malnutrition are common and it is in these areas that the vital role of nutrition in health is demonstrated most strikingly The importance of nutrition in growth and development, and in the maintenance of physical, mental and emotional well being throughout life, is attested by natural experiments in endemic areas of poor nutrition as well as by planned laboratory experiments with human volunteers Minot s statement (2) that the history of the world might be written in terms of nutrition rather than in terms of epidemics, as in Hans Zinsser's book *Rats, Lice and History*, does not seem to be an exaggeration

The importance of nutrition in conditions of physio logic stress i e , in growth, pregnancy and lactation, has been well documented Recent investigation indicates a close relationship between nutrition and many forms of pathologic stress such as severe infections or trauma Relationships between nutrition and some of the degen erative diseases, for example atherosclerosis and hypertension, and even between nutrition and neoplasia have been demonstrated It is in this wide variety of pathologic states that nutritional diagnosis assumes paramount importance in well fed population groups In rehabilitation

sense as meaning knowledge of the essential chemical substances which must be included in the diet and application of this knowledge to dietotherapy. The science of nutrition embraces a much wider field. Knowledge of the role of essential nutrients in metabolism, which includes the whole realm of nutritional biochemistry, is vital in the understanding of normal bodily function and the many disturbances which occur in disease. Many types of disease, whether infectious, metabolic or degenerative, influence the nutritional state of the patient and, in turn, nutrition influences the prevention, development and regression of many pathologic states.

Nutritional diagnosis means much more than the detection of some overt deficiency disease, a concept prevalent some years ago. Today, it is essential to think less in terms of specific deficiency states and more in terms of disturbances in the biochemical reactions of the body. The diet must furnish the potential energy for basal metabolic processes and for physical activity and, also, all of the chemical substances needed for manufacture of new tissue. Recent investigations, using isotopic techniques, have indicated that the components of cells are constantly being broken down and reconstituted, requiring continuous replenishment with essential nutrients (1). Nutritional diagnosis implies therefore evaluation of the biochemical milieu within and outside of the cells, as well as detection of abnormalities of function and structure of the organs and tissues of the body. Recent studies of the role of mitochondria and other cellular units in oxidative metabolism link cytology and biochemistry closely together and may lead to better correlation between pathologic anatomical changes and biochemical abnormalities of body tissues and fluids.

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GENERAL OBSERVATIONS

NUTRITIONAL diagnosis is not easy in spite of the mass of information accumulated in recent decades Variation among individuals is great and the dividing line between normal and abnormal is not clear-cut This might be anticipated since nutritional attributes and functions would be expected to show normal distribution curves as do other physiologic variables Nor should this be discouraging since similar difficulties are found in all fields of biological investigation and similar problems are encountered in the diagnosis of cardiac, pulmonary or gastrointestinal disease Basic scientific knowledge coupled with astute clinical observation forms the foundation of diagnostic acumen Adeptness in the art of obtaining a medical history, keenness in detecting minor physical deviations from the normal judicious choice of laboratory procedures, and ability to correlate all findings into a comprehensive whole, are the "sine qua non" for nutritional diagnosis as for diagnosis in other fields of medicine

It is essential to know nutritional requirements and the function of nutrients in health and to be cognizant of the potential influence of disease on the requirement and utilization of nutrients Knowledge of the effects of an inadequate supply of essential dietary factors is a requisite for accurate diagnosis Cultivation of nutrition "consciousness" and an awareness of the nutritional aspects of biochemistry and metabolism is almost obligatory

from all types of injury, close attention to nutritional problems reaps a rich reward decreasing morbidity and mortality

The frequency with which nutritional defects are encountered is not appreciated by many physicians A casual walk through the wards or private rooms of any large hospital will attest the high incidence of nutritional problems Malnutrition is usually obvious in the patient with cirrhosis of the liver, advanced pulmonary tuberculosis or chronic ulcerative colitis It is recognized readily that maintenance of adequate nutrition is difficult during the recovery period after total gastrectomy or resection of the colon It is perhaps less obvious that nutritional problems are common and of significant import in the patient with *congestive heart failure rheumatic fever, peptic ulcer or* some type of allergic state Similar examples could be cited in all branches of medicine

In view of the frequency and importance of nutritional problems in medical practice, a review of the methods and procedures currently available for nutritional diagnosis and of criteria useful in the evaluation of nutritional status seems warranted Nutritional diagnosis is not so exact that abnormalities of cellular chemistry can be detected with precision Much remains to be learned and new tools and methods must be developed Nevertheless progress has been rapid The present state of knowledge and areas requiring future development will be summarized in the *sections that follow*

These must be sought by adroit questioning and confirmed or discarded by physical examination and appropriate laboratory procedures

Findings in childhood which suggest nutritional deficiency include failure to grow or gain weight, poor appetite, lethargy, disinterest in play and irritability In adults, some of the common complaints which may be associated with malnutrition are easy fatigability, loss of weight and strength and anorexia Symptoms may indicate dysfunction of any of the bodily systems Photophobia, burning of the eyes, lacrimation and night blindness may be observed Soreness of the lips, tongue and angles of the mouth, digestive disturbances and diarrhea are not infrequent. Palpitation, dyspnea and edema may be due to nutritional deficiencies Parasthesias and other sensory changes, particularly of the fingers and toes, easy bruising and dryness and pigmentary changes in the skin are often encountered. Since all of the above symptoms may occur in diverse pathologic conditions, all potential causative factors must be investigated.

The past medical record is valuable in indicating recent recurrent or chronic disease or trauma, which may be related to the findings observed or affect nutritive state Religious and social customs occupation and economic status, in fact, practically all aspects of the environment whether geographical, physical or educational may exert an influence on food habits and on nutrition

The family history, too provides informative data. Family size, the record of illnesses and death, the occurrence of stillbirths, may shed light on nutritional problems Fertility and the course of pregnancy are influenced by diet Delayed puberty, amenorrhea and impotence may be due to undernutrition or malnutrion as well as to other causes

MEDICAL HISTORY

The medical history is of great importance in detecting the presence of disease which may influence nutritional status and in eliciting symptoms which suggest nutritional abnormality The physician should be aware of the physiologic, pathologic, or therapeutic situations which are prone to induce nutritional deficiency or excess

Nutritive requirements may be increased in many diseases, particularly those in which basal metabolic rate is increased such as febrile illnesses, hyperthyroidism and certain other endocrinopathies, leukemia and polycythemia and diseases of the heart and lungs associated with severe dyspnea In a number of psychotic states, abnormal physical activity increases total metabolic needs Many diseases and some therapeutic agents interfere with ingestion, digestion or absorption of food Diseases of the gastrointestinal tract and the myriad conditions associated with anorexia, nausea, vomiting and diarrhea belong in this category Interference with the utilization of nutrients may be observed in hepatic disease, hypothyroidism, advanced renal disease, neoplasia, and following radiation therapy Severe injuries, shock, and chronic anemic states profoundly affect metabolic processes Nutrients may be lost from the body in conditions associated with polyuria, in therapeutic diuresis, and following administration of certain drugs

Nutritional excess is best exemplified by an overabundance of calories but metabolic disturbances and therapeutic agents may lead to syndromes in which excessive amounts of nutrients particularly certain minerals and vitamins accumulate in the tissues

The physician must know the symptoms and signs associated with an inadequate or overabundant supply of each of the chemical substances essential in human nutrition

TABLE 1

Dietary Record

Name

Age Sex Height Weight

Diet—Previous 24 hours

Breakfast		Noon Meal		Evening Meal		Between Meals	
Food	Amt.	Food	Amt	Food	Amt.	Food	Amt

Diet History—Foods used— Amount and frequency (day, week or month)

Meat
- Fresh (beef veal lamb pork)
- Fish
- Fowl
- Liver
- Prepared salt

Eggs

Milk
- Whole, skim, evaporated butter milk
- Cheese

Nuts and Peanut Butter

Fats
- Butter oleomargarine
- Mayonnaise
- Cream

Vegetables
- Legumes, dried
- Legumes fresh
- Green
- Yellow
- Potatoes, Irish
- Potatoes Sweet
- Tomatoes
- Other vegetables

Fruits
- Citrus
- Others, canned
- Others fresh
- Juices

Breads
- Bread (kind)
- Biscuit
- Corn bread
- Crackers

Cereals
- Rice
- Grits
- Macaroni spaghetti
- Cooked
- Prepared

Sweets
- Syrup molasses
- Jams, jelly
- Candy
- Desserts

Beverages
- Coffee
- Tea
- Soft drinks
- Alcohol

Other food

Food dislikes

Number of meals eaten per day

Vitamin preparations

DIETARY HISTORY

The dietary record is an important part of the medical history Although a quantitative estimate of recent and habitual food intake may be difficult to obtain, it is usually possible to glean sufficient information to evaluate the diet from a qualitative standpoint Several methods of obtaining dietary information have proved useful A simple procedure is to ask the patient to recall the kinds and approximate amount of foods eaten in the previous 24 hours and to ascertain whether or not this is representative of the usual dietary pattern The accuracy of the 24 hour diet record may be checked by the use of a list of common foods (divided into several principal groups), the patient being asked to indicate how often each is included in the diet (Table 1) Another method of obtaining dietary information is to have the patient keep a record of all food eaten, including amounts, for a period of several days to a week These records are then evaluated by comparison with some dietary standard

Difficulties in eliciting accurate dietary information are numerous Many persons do not remember what they eat and have a poor idea of quantity, some tend to exaggerate, while others underestimate Patients may be ashamed of the meagerness of their diets and conceal this information, others may describe their food intake in terms of what they believe the physician considers desirable In spite of these and other pitfalls the dietary record often suggests deficits which can be investigated further by clinical or laboratory tests

Evaluation of the diet from a qualitative standpoint can be carried out easily by the physician in his office by using some simple standard such as that shown in Table 2 This was devised for appraisal of the diet of an adult in the United States Similar tables can be prepared which are

applicable to children or to other countries If it is desirable to obtain more detailed information as to the quantity of specific nutrients in the diet, tables of food composition are available which permit such calculation (3)

Many dietary standards have been formulated by national and international groups (1) The purpose of these standards and the philosophies on which they are based have varied widely In the United States, the Recommended Dietary Allowances of the Food and Nutrition Board of the National Research Council (1a)) have been used extensively (Table 3) These allowances represent the amounts of essential nutritive substances which appear desirable for the maintenance of good nutrition in essentially all healthy persons in the United States They are more than minimum requirements and represent goals toward which to strive in planning diets and food supplies If these allowances are used in quantitative evaluation of the diet of an individual, they must be interpreted correctly A person whose diet meets recommended allowances will rarely exhibit nutritional deficiency, except in the presence of some disease which influences requirement or utilization of nutrients On the other hand, if a person s diet fails to fulfill recommended allowances, this does not necessarily signify nutritional deficiency A nutrient intake considerably below recommended allowances suggests inadequate intake and requires additional investigation

Dietary evaluation has been used extensively as one aspect of the appraisal of nutritional status of population groups Dietary surveys are valuable particularly in areas where food supply is limited and have served as a basis for planning nutrition programs Changes in food consumption of population groups can be followed with this

TABLE 2

STANDARD FOR EVALUATION OF DIETARY PATTERN IN ADULT SUBJECTS*

Food Group	Amount Recommended Daily	Primary Purpose
1 Milk Cheese and ice cream can replace part of milk	Two or more servings (1 cup or 8 oz each)	Protein Calcium Riboflavin Vitamin A
2 Meat Beef veal pork, lamb poultry fish eggs. Dry beans and peas and nuts can be used as alternates	Two or more servings (at least 2 oz each)	Protein Thiamine Riboflavin Niacin Iron
3 Vegetables and fruits Should include a) a dark green or deep yellow vegetable at least every other day for vitamin A b) a citrus fruit or other fruit or vegetable rich in vitamin C daily c) other fruits and vegetables including potatoes	Four or more servings (½ cup each)	Vitamin A Ascorbic acid Iron Thiamine Riboflavin Niacin Trace minerals
4. Bread and cereals whole grain, enriched or restored	Four or more servings (1 slice bread or ½ cup cereal)	Thiamine Niacin Iron Protein Riboflavin
Other foods—sugars, fats oils, including butter or fortified margarine for vitamin A		Calories Vitamin A

* For further details refer to Essentials of an Adequate Diet. Agriculture Information Bulletin No 160 Washington D C. Agricultural Research Service, U S Dept. Agriculture, November 1956

survey method Selection of proper standards with which to judge the nutritive value of diets is important, standards applicable in one community may require modification in another Methods and procedures which may be useful in dietary surveys are discussed in several recent reviews (5)

PHYSICAL EXAMINATION

A thorough and detailed physical examination can give much information relative to nutritional status although laboratory procedures may be needed to substantiate diagnosis It should be kept in mind that nutritional deficiencies are often multiple and that similar lesions may be caused by an inadequate supply of more than one nutrient Furthermore, the type of physical abnormality encountered varies according to the duration and severity of the deficiency There are almost no pathognomonic findings, a situation which holds in other diagnostic fields However, a combination of symptoms and signs, together with historical and laboratory data will permit accurate diagnosis in most instances

General inspection yields much valuable information, in fact it is often possible to tentatively appraise the whole nutritional problem if observation is sufficiently keen Observation begins when the patient is first seen in the home, office or hospital and while the history is being recorded The physician gains an impression of the patient s general health, vigor, intelligence and emotional reactions Gross defects in caloric nutrition are obvious excessive fat pads denote obesity, absence of subcutaneous fat indicate excessive leanness folds of sagging inelastic skin suggest marked loss of weight The stature general skeletal development, bulk of muscle color and texture of skin and hair are noted almost subconsciously Edema

TABLE 3

FOOD AND NUTRITION BOARD NATIONAL RESEARCH COUNCIL
RECOMMENDED DAILY DIETARY ALLOWANCES[1] REVISED 1958

DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY PERSONS IN THE U.S.A.

(Allowances are intended for persons normally active in a temperate climate)

	Age Yea s	Weight kg (lb)	Height cm. (in.)	Calories	Protein gm.	Calcium gm	Iron mg	Vitamin A I U	Thiam mg	Ribo mg	Niacin[2] mg equ s	Asc Acid mg	Vitamin D I U
Men	5	0 (154)	175 (69)	3"00[3]	70	0 8	10	5000	1 6	1 8	21	5	
	45	70 (154)	175 (69)	3000	70	0 8	10	5000	1 5	1 8	20	5	
	65	70 (154)	175 (69)	550	70	0 8	10	5000	1 3	1 8	18	75	
Women	5	58 (1 8)	163 (64)	2300	58	0 8	1	5000	1 2	1 5	17	0	
	45	58 (128)	163 (64)	200	58	0 8	12	5000	1 1	1 5	17	70	
	65	58 (1 8)	163 (64)	1800	58	0 8	12	5000	1 0	1 5	17	70	
	Pregnant (second half)			+ 300	+ 0	1 5	15	6000	1 3	2 0	+ 3	100	400
	Lactating (850 ml. daily)			+1000	+40	2 0	15	8000	1 7	2 5	+ 2	150	400
Infants[4]	0-1/12[4]				See Footnote								
	2/12-6/12	6 (13)	60 (24)	kg.x120		0 6	5	1500	0 4	0 5	6	30	400
	7/12-12/12	9 (20)	70 (28)	kg x100		0 8	7	1500	0 5	0 8	7	30	400
Children	1 3	12 (27)	87 (34)	1300	40	1 0	7	000	0 7	1 0	8	35	400
	4 6	18 (40)	109 (43)	1700	50	1 0	8	500	0 9	1 3	11	50	400
	7 9	27 (60)	1 9 (51)	?100	60	1 0	10	3500	1 1	1 5	14	60	400
	10-12	36 (9)	144 (57)	,500	70	1 2	12	4500	1 3	1 8	17	75	400
Boys	13 15	49 (108)	163 (64)	3100	85	1 4	15	5000	1 6	2 1	21	90	400
	16-19	63 (139)	175 (69)	3600	100	1 4	15	5000	1 8	2 5	5	100	400
Girls	13-15	49 (108)	160 (63)	600	80	1 3	15	5000	1 3	2 0	17	80	400
	16-19	54 (1"0)	162 (64)	2400	75	1 3	15	5000	1 2	1 9	16	80	400

(1) The allowance levels are intended to cover ind v dual variations among most normal persons as they live in the United States under usual envi onmental stresses The recommended allowances can be attained with a var ety of common foods providing other nutrients for which human requirements have been less well defined See text for more detailed discussion of allowances and of nu trients not tabulated

(2) *Niacin equivalents include* dietary sources of the preformed vitamin and the precursor tryptophan 60 milligrams tryptophan equals 1 milligram niacin

(3) Calorie allowances apply to ind viduals usually engaged in moderate physical activity (page 2) For office workers or others in sedentary occupat ons they are excessive Adjustments must be made for variations in body size age physical activity and environmental temperature

(4) See text for discussion of infant allowances The Board reogn es that human milk is the natural food for infants and feels that breast feeding is the best and desired procedure for meeting nutrient requirements in the first months of life No allowances are stated for the first month of life Breast feeding is particularly indicated during the first month when infants show handicaps in homeostasis due to d fferent rates of maturation of digestive excretory and endocrine functions Recommendations as listed pertain to nutrient intake as afforded by cow s milk formulas and supplementary foods given the infant when breast feeding is terminated Allowances are not given for prote n during infancy

TABLE 4

Physical Signs Which May be Associated With Malnutrition

Apathetic appearance

Hair dry "staring"
- Dyspigmented

Skin, facial
- Seborrhea, nasolabial
- Seborrhea, other
- Erythema
- Folliculosis

Skin, general
- Dryness and scaling
- Crackled skin
- Hyperpigmentation
- Depigmentation
- Follicular keratosis
- Perifolliculosis
- Acneiform eruption
- Thick, pigmented pressure points
- Purpura and petechia
- Bluish red cold extremities
- Pellagraform lesions
- "Crazy pavement" dermatitis
- Telangiectasis
- Redness of palms
- Nails, brittle flaking, ridging spoon shaped

Eyes
- Bitot s spots
- Canthi fissures
- Circumcorneal injection
- Conjunctival injection
- Lids, blepharitis follicular hypertrophy

Lips and mouth
- Angular lesions
- Angular scars
- Cheilosis
- Pallor
- Ulcers of mouth

Tongue
- Papillary atrophy
- Papillary hypertrophy
- Magenta color
- Red tip and/or sides
- Fissures
- Erosions or ulcers
- Serrations and swelling

Teeth
- Caries
- Edentulous
- Dentures
- Fluorosis

Gums
- Marginal redness
- Marginal swelling
- Bleeding

Thyroid
- Enlarged (colloid goiter)

Parotid gland bilateral enlargement

Neuromuscular
- Calf tenderness
- Loss of ankle or knee jerks
- Plantar dysesthesia
- "Burning feet"
- Motor weakness, paralysis
- Vibratory sense lost
- Position sense lost
- Hypesthesia and anesthesia
- Tetany

Skeletal
- Posture
- Frontal or parietal bosses
- Protuberant abdomen
- Harrison s groove
- Knock knees
- Bowlegs
- Enlarged wrists
- Enlarged costochondral junctions
- Flaring ribs
- Winged scapula
- Abnormalities of sternum

Cardiovascular
- Hypotension
- Bradycardia or tachycardia
- Cardiac enlargement failure
- Abnormalities of rhythm
- Murmurs

Edema

Liver
- Enlarged nodular

of marked degree is readily detected The general attitude and behavior of the patient, alertness or apathy, anxiety or depression, the facial expression, manner of speech and type of voluntary movements, all contribute to solution of the diagnostic problem This is particularly true when severe malnutrition is suspected, in starvation and severe protein deficiency, depression, apathy and lassitude are characteristic findings Differences in physiological and emotional reactions among various racial groups and among individuals must be considered in reaching an evaluation Observation of the spontaneous behavior of children has been found to be most useful in appraising nutritional status Lassitude, lack of interest and absence of spontaneous play are common in malnutrition In children, too, posture may reflect nutriture a forward slump of the head, kyphosis, lordosis, winged scapula and pot belly, all of which are expressions of poor muscle tone, are observed frequently among those who are poorly nourished

Detailed physical examination of all systems of the body should follow general inspection When nutritional diagnosis is applied to population groups, especially in large or rapid nutrition surveys, attention is directed particularly to the superficial tissues, the skin, hair, mucocutaneous junctions, eyes, and buccal mucous membrane

Schedules have been prepared for use in such nutritional appraisal (6, 7) Some of the physical findings commonly associated with malnutrition which may be searched for in nutrition surveys are given in Table 4 These abnormal signs and symptoms are also useful in evaluating the nutritional status of the individual patient It is obvious that many of these findings are non specific and that some are more closely related to malnutrition than others The presence of several abnormalities is

TABLE 5 (Continued)

Vitamin B_6 deficiency
- Seborrheic dermatitis
- Glossitis
- Angular stomatitis
- Peripheral neuropathy

Folic acid deficiency
- Weakness and pallor
- Glossitis—redness, abnormalities of papillae
- Diarrhea, steatorrhea

Vitamin B_{12} deficiency
- Weakness and pallor
- Glossitis—redness, abnormalities of papillae
- *Subacute combined sclerosis*
- Peripheral neuropathy

Ascorbic acid deficiency
- Purpura, petechiae, ecchymoses
- Red, swollen, bleeding gums
- Perifolliculosis
- Poor wound healing

Vitamin D deficiency
- Craniotabes
- Frontal and parietal bosses
- Enlarged joints (wrists and ankles)
- Harrison's groove
- Enlarged costochondral junctions
- Deformities of sternum
- Bowlegs or knock knees
- Osteomalacia

Vitamin K deficiency
- Hemorrhagic manifestations in *jaundice or in the newborn*

Calcium deficiency
- Paresthesias
- Carpo-pedal spasm
- Convulsions
- Positive Chvostek's and Trousseau's *signs*

Iodine deficiency
- Simple goiter

Iron deficiency
- Weakness and pallor
- Chronic glossitis
- Koilonychia

Magnesium deficiency
- Gross muscle tremor
- Delirium

Potassium deficiency
- Muscular weakness, hypotonia
- Flaccid paralysis
- Paralytic ileus
- Cardiac or respiratory failure

Sodium deficiency
- Weakness, apathy
- Anorexia, nausea, vomiting
- Muscle cramps
- Peripheral circulatory collapse

TABLE 5

SYMPTOMS AND SIGNS SUGGESTIVE OF DEFICIENCY OF CERTAIN NUTRIENTS

Caloric deficiency
- Underweight and underheight
- Weight loss
- Wasting of tissues

Protein deficiency—adults
- Weight loss
- Wasting of muscles
- Enlarged liver
- Edema

Protein deficiency—infants and children (*Kwashiorkor*)
- Growth retardation
- Depigmentation hyperpigmentation of skin
- Dyspigmentation of hair
- Enlarged liver
- Edema
- Peevish mental apathy

Vitamin A deficiency
- Night blindness
- Xerosis conjunctivae
- Bitot s spots
- Dry scaling skin
- Follicular hyperkeratosis

Thiamine deficiency
- Burning soles of feet
- Numbness and tingling of toes
- Calf muscle tenderness
- Hyperesthesia or hypesthesia of feet and legs
- Loss of vibratory sense
- Absent patellar and Achilles reflexes
- Motor weakness (squat test)
- Edema
- Advanced polyneuropathy
- Beriberi heart disease
- Wernicke s encephalopathy
- Retrobulbar neuritis
- Central ophthalmoplegia

Riboflavin deficiency
- Photophobia lacrimation burning and itching of eyes
- Soreness of lips and tongue
- Circumcorneal injection and corneal vascularization
- Cheilosis
- Angular maceration and fissures
- Glossitis—purplish color abnormalities of papillae
- Nasolabial seborrhea

Niacin deficiency
- Soreness and burning of tongue
- Chronic diarrhea
- Glossitis—redness swelling serrations abnormalities of papillae
- Pellagrous dermatitis
- Vaginitis and proctitis
- Mental changes—anxiety hallucinations, depression disorientation
- Encephalopathic states

TABLE 6

LABORATORY PROCEDURES USEFUL IN NUTRITIONAL DIAGNOSIS

Nutrient	Laboratory test	Normal findings	Findings suggestive of deficiency or other abnormality
Protein	Concentration of serum proteins	6-8 gm/100 ml	$<$6 gm/100 ml
	Concentration of serum albumin	4-5.5 gm/100 ml	$<$4 gm/100 ml
	Nitrogen balance	0 or positive	Negative
(Kwashiorkor)	Pancreatic enzymes in duodenal juice	Present	Absent
	Liver biopsy	Normal	Fatty infiltration necrosis and/or fibrosis
Carbohydrate	Glucose tolerance	Blood glucose concentration Fasting $<$130 mg/100 ml	Elevated blood glucose in diabetes
		Maximum $<$180mg/100ml 3 hr = or $<$fasting	Little increase in blood glucose in malabsorption
Lipids	Serum cholesterol concentration	Uncertain (200 mg/100 ml?)	Elevated in certain diseases (See page 56)
	Absorption I^{131}	Marked rise I^{131} in serum Fecal I^{131} low	Low serum and high fecal I^{131} in malabsorption syndromes
	Fat balance (diet 100 gm fat)	$<$5% fat in feces	$>$5% fat in feces
	Vitamin A tolerance	Increase serum Vitamin A to $>$200 μg%	Minimal rise serum Vitamin A in malabsorption

more significant than a single deviation from normal Interpretation is not easy and must be considered in conjunction with the dietary history and laboratory tests Some of the findings which are suggestive of specific nutritional deficiency are given in Table 5 and will be discussed in detail in subsequent sections

A number of laboratory procedures have been developed which are useful in evaluating nutritional status While these will be considered subsequently in the discussion of each of the essential nutrients, a summary of normal values and of changes which may be observed in malnutrition is given in Table 6

GROWTH OF INFANTS AND CHILDREN

In nutritional diagnosis in infants and children, appraisal of growth and development in relation to age and sex is of great importance All types of nutritional deficiency may retard the rate of growth whether the deficiency represents an inadequate supply of calories, protein, vitamins or minerals Growth rate is influenced, too, by disease and it is necessary to determine whether an inadequate food intake, some pathologic process, or both, are responsible for retardation

Assessment of growth implies a standard with which to compare the subject being examined Unfortunately, present standards are far from precise and the optimal rate of growth remains unknown The standards which have been developed by investigators at Iowa and Harvard Universities (8) or the Wetzel grid (9) are to be preferred to height weight age tables in evaluation of growth rate Genetic and environmental factors must always be considered in the use of such standards In any event, a single record of height and weight at a given age is of much less value than a long term record, since the latter

TABLE 6 (Continued)

Nutrient	Laboratory test	Normal findings	Findings suggestive of deficiency or other abnormality
Riboflavin	Riboflavin concentration in erythrocytes	>20 μg 100/ml	<14 μg 100/ml
Niacin	Urinary excretion N'Me and pyridone on test diet (See page 115)	>5 mg in 24 hrs	<3 mg in 24 hrs
Vitamin B_6	Xanthurenic acid excretion after 10 gm d l tryptophan	<30 mg. in 24 hrs	>50 mg in 24 hrs
	Blood urea nitrogen 12 hrs after 30 gm alanine	Normal	Elevated
Folic Acid	Complete blood count	Normal	Anemia
	M C V *	80-95 cu microns	>100 cu microns
	Bone marrow	Normal	Megaloblastic
	Urinary excretion after 5 mg folic acid orally	>2 mg	<1.5 mg in malabsorption
Vitamin B_{12}	M C V *	80-95 cu microns	>100 cu microns
	Bone marrow	Normal	Megaloblastic
	Schilling test (see page 130)	Excretion Co* B_{12} >6%	Excretion Co* B_{12} <2%
	Serum B_{12}	>100 μ μg/ml	<80 μ μg/ml

*M C V — Mean Corpuscular Volume.

TABLE 6 (Continued)

Nutrient	Laboratory test	Normal findings	Findings suggestive of deficiency or other abnormality
Sodium	Serum sodium concentration	140 mEq/liter	Usually decreased in deficiency increased in retention
Potassium	Serum potassium concentration	4.2 mEq/liter	Often decreased in deficiency increased in retention (See page 77)
Calcium	Serum calcium concentration	5.0 mEq/liter	Decreased
Iron	Mean corpuscular hemoglobin concentration	32-34%	<30%
	Serum iron concentration	80-180 μg/100 ml	<50 μg/100 ml
	Serum iron binding capacity	300-360 μg/100 ml	>400 μg/100 ml
	Hemosiderin in bone marrow	Present	0 to trace
Vitamin A	Serum vitamin A concentration	30-50 μg/100 ml	<20 μg/100 ml
	Serum carotene concentration	75-200 μg/100 ml	<50 μg/100 ml
Thiamine	Urinary thiamine excretion after giving 1 mg parenterally	100-200 μg in 4 hrs	<50 μg in 4 hrs
	Carbohydrate index (See page 107)	<15	>15

is indicative of rate of growth of the child in question In a sense, the child becomes his own control and improvement or retrogression can be appreciated readily The nutritional or other cause of change should then be determined Another method of evaluating growth is estimation of skeletal maturation Several procedures for this have been devised (10)

Many studies have indicated the important influence of nutrition on the course of pregnancy and on the condition of the infant at birth (11) The incidence of still births and premature births and the birth weight of full term infants is affected by maternal nutritional state Data relative to these findings have been collected in certain areas and used in partial evaluation of nutritional status of population groups

Determination of height and weight of school children also gives information which has proved useful in nutrition surveys The rate of growth of children is a sensitive index of food supply and dietary practices Conclusions from such data will be valid only if satisfactory standards are available for the population group in question or if comparison can be made between several homogeneous sections of the population Changes which occur following institution of programs designed to improve nutrition will also be informative

TABLE 6 (Continued)

Nutrient	Laboratory test	Normal findings	Findings suggestive of deficiency or other abnormality
Ascorbic acid	Plasma ascorbic acid concentration	0 6 to 1 0 mg/100 ml	<0 1 mg/100 ml
	Ascorbic acid concentration in WBC—platelet layer	20-30 mg/100 ml	<2 mg/100 ml
(Infants)	Serum concentration 4 hrs after parenteral dose of 200 mg	>0 4 mg/100 ml	<0 4 mg/100 ml
Vitamin D (infants)	Alkaline phosphatase	5 15 Bodansky Units	>20 Bodansky Units
	Serum phosphorus	2 5 3 6 mEq/1	<2 5 mEq/1
Vitamin E	Serum tocopherol concentration (adults)	1 0 1.2 mg%	Decreased
	(infants)	0.23 0 43 mg%	Decreased
	Erythrocyte hemolysis	Normal	Increased
Vitamin K	Prothrombin time	10-15 seconds	Prolonged

further knowledge The height weight standards used currently represent arithmetic averages of findings in selected population groups In most instances, data were obtained at the time of application for insurance, the individuals being weighed and measured in ordinary clothes (14) The inexactness of such standards is apparent Clothing and height of heels introduce appreciable variables

In some standards, average weights are given for light, medium and heavy body types No accurate method of determining body build is available although a rough appraisal can be made by the experienced clinician Measurement of bi-cristal (bi iliac) diameter is of assistance (15) Determination of bi acromial diameter is also useful but is more difficult to obtain accurately, due to the influence of posture on this measurement

Genetic variations and environmental factors, such as climate, should be taken into account in height weight appraisal Available standards are useful if interpretations are made with appreciation of their inexactness An individual who is less than "standard" weight may be lean, or have poorly developed muscles or a small skeleton An individual whose weight exceeds the standard may be excessively fat, or may have a large muscle mass or a large skeleton

It would be desirable to estimate the relative proportion of the components of the total body mass, namely, bones, muscles, extracellular fluid and adipose tissues Recently, biophysical and biochemical methods have been devised for estimation of body composition and have been applied in evaluation of leanness and fatness in man (16) Total body fat may be estimated by determining the specific gravity of the body, by estimating total body water, and by measurement of the thickness of subcutaneous tissues,

CALORIC NUTRITION

DIAGNOSIS of caloric undernutrition or over nutrition is relatively easy if deviation from the normal is great but minor deviations cannot be determined with precision The dietary history is of some assistance in estimating the extent of caloric deficit or surplus in spite of the difficulties in ascertaining daily food consumption accurately Knowledge of energy requirements according to age, sex, body size and physical activity is necessary for interpretation of findings Approximate caloric needs of populations groups, and to a lesser extent of individuals, may be determined with the use of schedules prepared by several national and international groups (4, 12) The requirement for an individual may be obtained more accurately by calculating his basal metabolic needs and adding the amount required for physical activity The importance of calories during growth was emphasized by Macy and Hunscher (13) who pointed out that as few as *10 calories per kilogram of body weight per day* may may make the difference between progress and failure

METHODS FOR EVALUATION

In evaluating height and weight in children, growth charts may be used but interpretation should be cautious Ideal weight for height is not known for either children or adults In adults, desirable weight may be considered to be the average weight, for a given height and type of body build, of persons 25 years of age who are in good health More precise definition of ideal weight must await

Muscular development of an individual can be esti mated by determining the breadth of the muscular seg ments of soft tissue x rays of the extremities Some infor mation can be obtained by measurement of limb circum- ference if thickness of the skin and subcutaneous fat is determined at the same time

With application and improvement of the methods in- dicated above, diagnosis of caloric nutriture should be- come more exact It is anticipated that more adequate "norms" as "standards" will be developed for population groups of varying genetic potentialities and environ- mental situations

CALORIC OVERNUTRITION

The serious medical hazard of obesity is attested by insurance data which indicate that if the death rate of the standard risk is taken as 100, the mortality of men who are moderately overweight is 142 and of those mark- edly overweight 179 The respective values for women are 142 and 161 (21) Overweight as judged by standard height weight age tables does not necessarily mean obesity which should be defined as a disproportionately large fat content of the body The incidence of diseases of the heart, arteries and kidneys, of diabetes mellitus, of gallbladder disease, and even of neoplasia is increased in persons who are overweight (21) Important information might be obtained by application of the newer methods of esti- mating body composition in examination of overweight persons in whom various pathologic conditions have de- veloped The recent implication of lipids in the patho genesis of atherosclerosis has stimulated interest in this field (See p 53) Much remains to be learned about the role of excessive fat accumulation and of lipid me- tabolism in the pathogenesis of disease However, suffi

muscle and bone in x ray photographs (16, 17) Mc Cance, Williamson and associates (18) calculated body fat either from total body water, or by subtracting the weight of the extracellular fluid, cell mass and minerals in the skeleton, from the total body weight Minerals were esti mated as 7% of the fat free body The weight of cellular tissues was determined by assuming that cells contain 67% water and estimating intracellular water as the difference between total body water and extracellular space Keys and associates (19) suggested estimation of cell or 'active' tissue mass as body weight less fat, extracellular fluid and bone mineral, fat being determined from body density These methods are of importance in research and may be used as criteria for evaluating simpler procedures which the clinician can apply

An indirect method for estimation of fatness or leanness which seems promising is measurement of the thickness of skin folds in several areas of the body with specially constructed calipers Good correlation has been demon strated in adult males between findings with this method and determination of specific gravity of the body (16 17) Correlation has also been demonstrated between pinch caliper and x ray measurements of the thickness of skin and subcutaneous fat (20) The use of skinfold measure-ments as criteria for evaluating fatness or leanness of the body requires further study Data available at present suggest that measurements of skin fold thickness at two sites are of value the back of the right upper arm and below the tip of the right scapula Details of the pro cedure are given in a recent publication in which other anthropometric measurements for characterization of nu tritional status are also discussed (15) Skinfold measure-ments in a large group of young American males, white and negro, are included in this report

latory findings include bradycardia, hypotension, reduced peripheral circulation and decreased venous pressure. The body temperature is lowered and there is a decrease in the reactivity of the organism to various stimuli. Neurological examination often shows diminished or abolished deep tendon reflexes but sensory mechanisms are maintained in most instances. Signs of depressed function of the endocrine system, particularly of the sex glands, are common, amenorrhea, sterility and loss of libido being frequent findings. The patient looks, feels, and acts prematurely old. Polyuria, increase in fluid intake and salt hunger are often observed. Osteomalacia is an occasional finding in prolonged starvation. Edema is frequently encountered and may mask the extent of decrease in body weight. If protein deficiency is severe, the edema may be even more extensive and anemia, often of macrocytic type, may be present.

Signs of vitamin deficiency occur only if the diet has been deficient in these factors. Starvation, as observed in concentration and prisoner of war camps, particularly in the Orient, was accompanied in many instances by peripheral neuropathies, retrobulbar neuritis, deafness, encephalopathy and other neurologic syndromes. Some manifestations responded to therapy with B complex vitamins while others were unaffected.

In severe prolonged undernutrition, basal metabolic rate declines, the decrease in basal oxygen consumption applies to active metabolizing tissue as well as to the whole organism. The fasting blood sugar may be low and tolerance for glucose diminished. In semi starvation experiments with human volunteers blood pyruvate rose to abnormally high levels after exercise (19). Studies of body composition in these experiments in which an average of 16 kg. in weight was lost in 24 weeks, indicated no

cient information is at hand to indicate the desirability of maintaining normal body weight and avoiding excessive fatness

CALORIC UNDERNUTRITION

Caloric undernutrition occurs primarily as a result of a limited food supply, exemplified by semi-starvation and starvation, and secondarily as a consequence of many pathologic states, particularly those associated with an increase in metabolism or with anorexia or gastrointestinal disturbances The loss of potential calories in diarrheal diseases, especially in steatorrheas, may be extensive In diabetes mellitus glycosuria is a manifestation of caloric loss

Caloric balance can be maintained over a fairly wide range of body weight and caloric intake in a given individual A continued loss of weight beyond 10% may be considered evidence of caloric deficit Weighing a patient at frequent intervals is the best single method of determining caloric balance although fluctuations may represent changes in fluid rather than in metabolic mass, especially in acutely ill patients

The primary findings in caloric undernutrition, in addition to weight loss, are wasting of muscles weakness and lethargy Nitrogen balance is negative and deficiency of protein complicates the clinical picture The previous state of nutrition, the character of the diet and the manifestations of primary disease, when such is present, influence findings

In severe starvation, apathy, weakness and wasting of muscles become extreme and the patient literally appears to be nothing but skin and bones Mental and emotional changes are common and are reflected in behavior Pigmentary changes in the skin have been observed Circu-

knowledge of the possible effects of malnutrition or its residues on susceptibility to, or on the course of, other diseases Simple undernutrition tends to have a favorable influence on diabetes and a detrimental effect on tuberculosis Psychological residues of starvation are probably of great importance but have received little study

significant change in bone mineral or in extracellular fluid, a marked decrease in body fat and a lesser but significant decrease in active metabolizing tissue On a percentage basis, the body contained less fat and muscle but more water This excess fluid may explain, at least in part, the occurrence of starvation edema For a review of the biochemical and physiological changes in starvation, reference is made to the compilation published by Keys and associates (19)

In caloric undernutrition, the extent of the weight loss is an important factor in prognosis If the loss is 30% or less in previously healthy persons, full recovery may occur with proper care A loss of more than 40% is serious, although recovery is at times possible

Caloric undernutrition which is secondary to disease may be manifested by many of the findings just described, in addition to the signs characteristic of the primary pathologic process Another finding worthy of emphasis is that starved persons are poor surgical risks Extensive loss of weight may lead to altered hepatic function, contracted blood volume reduced capacity to control infections and impaired wound healing Furthermore it is difficult to determine when rehabilitation is sufficiently advanced to undertake surgery

Knowledge of the residues of serious undernutrition, the late or permanent effects is limited Children seem to recover completely from caloric restriction if the duration is not more than a year or two Residues of severe or protracted malnutrition, in formerly healthy soldiers who had been in prison camps have included excessive fatigue, weakness, inability to maintain proper weight, general "nervousness," excessive sweating paresthesias visual defects including optic atrophy, hernias cardiac and gastrointestinal complaints and osteopathy There is little

growth is most rapid, and during the latter half of pregnancy and in lactation The recommended protein allowance for maintenance in adult life is 1 0 gm per kilogram of body weight daily (Table 3) The minimal requirement of the eight essential amino acids for adult men (22) and women (23) are shown in Table 7 Part of the requirement of phenylalanine may be supplied by tyrosine and part of the methionine requirement by cystine Sufficient nitrogen must also be furnished by the diet for manufacture of the nonessential amino acids Some investigations of the amino acid needs of infants have been reported (24) No precise information is available for childhood and adolescence

The quality of dietary protein is dependent on amino acid content Animal proteins which contain all the essential amino acids have greater biological value than do vegetable proteins which are often deficient in one or more of these amino acids Numerous methods, direct and indirect, have been suggested for determining the biological value of proteins These have been reviewed in a recent symposium (17) The proportionate requirements of essential amino acids for maintenance of nitrogen equilibrium in man appear to be similar to those of growing animals for maximum nitrogen retention Mitchell (17) has suggested the use of an "essential amino acid index" in assessing the nutritive value of food proteins This index shows a high correlation with biological value as obtained in animal experiments

Investigation has shown that not only must all the essential amino acids be included in the diet but they must be present at the same time and in the proper proportions Thus, the amino acid balance of the diet is a factor requiring consideration in evaluating protein nutrition (25) Recently an attempt has been made to devise a theo-

PROTEIN NUTRITION

Malnutrition due to an inadequate supply of protein of good quality is probably the most important deficiency syndrome in the world today other than caloric undernutrition Protein deficiency may be primary, or occur in association with caloric deficiency, or be secondary to a wide variety of pathologic conditions Deficiency is common in prolonged febrile illnesses, hyperthyroidism and other diseases associated with hypermetabolism It is encountered in the many conditions in which protein is lost from the body such as the nephroses, effusions into serious cavities, exudates and weeping wounds Deficiency is observed, also, in diseases which impair digestion or absorption and in metabolic disturbances which interfere with utilization Negative nitrogen balance commonly follows trauma such as fractures, burns and operative procedures and may persist for weeks Nitrogen loss may amount to as much as 0 6 gm per kilogram of body weight daily, which represents a loss of 3 75 gm of protein per kilogram

PROTEIN REQUIREMENT AND DIETARY EVALUATION

In approaching the diagnosis of protein deficiency, it is essential to know the requirement of protein and of the eight amino acids which have been found to be dietary essentials for man The minimal requirement of protein for the adult is in the neighborhood of 0 5 to 0 65 gm per kilogram of body weight daily Larger amounts are needed during the period of growth, being greatest when

retically optimal protein with proper balance of amino acids with which the intake of dietary protein may be compared (25a) This should prove useful in evaluating the protein supply of population groups or even of individuals Undoubtedly, revisions of this provisional "optimal" amino acid pattern will be forthcoming as it is tested under varying conditions

Schoenheimer (1) and others have demonstrated that proteins are constantly being broken down and reconstituted, and that there is a constant interchange between amino acids in tissue protein and free amino acids Accordingly, a continuous supply of amino acids is needed in the diet Sprinson and Rittenberg (26) have estimated that the time needed for half replacement of body protein in man is about 80 days The rate of amino acid exchange varies in different tissues the turnover in liver and plasma accounts for 41% of the total exchange in man Likewise, depletion of tissue proteins during the development of deficiency is not uniform some proteins being depleted more rapidly than others and some tissues more severely than others (17) An adequate supply of calories from non protein sources is important in proper utilization of protein so that amino acids may be spared for protein synthesis and other vital functions, rather than being utilized for energy

The functions of protein in the body are many Amino acids are used in the synthesis of cellular proteins of all tissues, of special proteins such as hemoglobin, albumin, globulin fibrinogen etc and in the formation of enzymes, hormones, and antibodies Amino acids are important in transmethylation and detoxification reactions some of them have lipotropic function In addition they may be deaminated and the remainder of the molecule transformed into glucose or fatty acids which are utilized for

TABLE 7#

AVERAGE MINIMAL REQUIREMENTS FOR ESSENTIAL AMINO ACIDS AS DETERMINED BY DIFFERENT WORKERS

	Isoleucine	*Leucine*	*Lysine*	*Phenylalanine*	*Sulfur containing Amino Acids* *Methionine*	*Cystine*	*Total*	*Threonine*	*Tryptophan*	*Valine*
				Average minimal needs milligrams per kilogram body weight						
Infants[24]	90	—	90	90*	{ 85	0	85 }	60	30	85
					{ 65	pres.	— }			
Men[22]	10 4	9 9	8 8	4 3**	1 5	11 6	13 1	6 5	2.9	8.8
				13.3***	13.2		13.2			
Women[23]	5.2	7 1	3 3	3 1****	4 7	0 5	5.2	3 5	2.1	9.2
					3 8	(2.2)	6 0			
					3 4	3 4	6.8			
					3 0	(4.2)	7.2			

(Reproduced from Protein Requirements, FAO Nutrition Studies No 16 Food and Agriculture Organization of the United Nations, Rome, 1957—reference 25a)

* Tyrosine present

** 15 9 mg tyrosine per kg—ratio of tyrosine to tryptophan equals 5 5

*** No tyrosine

**** 15 6 mg tyrosine per kg—ratio of tyrosine to tryptophan equals 7 4

Recent evidence indicates that 80-85% of the methionine requirement is replaceable by cystine and 70-75% of the phenylalanine requirement is replaceable by tryosine.

deficiency may be masked by a decrease in blood volume While determination of blood volume is difficult and not always satisfactory, estimation of total circulating serum albumin is a more accurate method of detecting protein depletion than is measurement of concentration of serum albumin Even small decreases in serum albumin represent loss of tissue protein of considerable magnitude On the basis of animal experiments, it may be assumed that each gram of decrease in total circulating albumin represents a loss of approximately 30 0 gm of tissue protein (28)

Several years ago, Harroun and associates (29) suggested estimating extravascular reserves of protein (interstitial fluid and lymph) by determining the response to rapid infusion of one liter of isotonic sodium chloride Normal persons showed an increase in plasma volume and in total circulating protein, while malnourished subjects showed a smaller increase in plasma volume and a decrease in total circulating protein Further evaluation of this procedure seems indicated

Electrophoretic analysis of serum proteins has not proved of value in the diagnosis of protein deficiency which accompanies caloric undernutrition (30) Studies of antibody response in subjects with abnormal levels of serum protein have failed to show a relationship between the concentration or distribution of serum protein fractions and the ability to form antibodies (31)

In protein deficiency, nitrogen balance is negative Since balance studies require special facilities they are more useful in research than in medical practice Furthermore, many difficulties are inherent in the interpretation of nitrogen balance data Simultaneous depletion and repletion of various compartments of body protein may

energy or stored as fat Thus, proteins are vital for growth, reproduction, maintenance of health and rehabilitation from injury

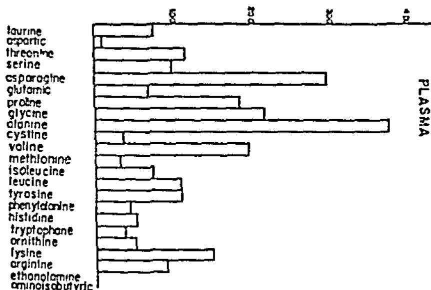
PROTEIN DEFICIENCY

In the diagnosis of protein malnutrition, the first steps are determination of the approximate dietary supply of protein from a quantitative and qualitative standpoint and recognition of the pathologic conditions which are prone to lead to protein deficiency Physical findings common to most protein deficiency syndromes are loss of weight (unless masked by edema), decrease in subcutaneous fat, weakness, muscle wasting, edema and accumulation of fluid in serous cavities Frequently, hypotension, brady cardia and pigmentary changes in the skin are observed and the basal metabolic rate may decrease Protein deficiency may lead to fatty infiltration and cirrhosis of the liver Anemia, which mav be normocytic or macrocytic, is a frequent accompaniment of chronic protein deficiency syndromes Protein deficiency increases the risk of surgery and is associated with poor healing of wounds

Heart disease of unexplained cause has been reported to be prevalent in certain areas of the world where pro tein malnutrition is common Gillanders (27) in South Africa has described heart failure in association with large, hypodynamic, dilated but often not hypertrophied hearts Whether protein deficiency is responsible for this syndrome or for the endomyocardial fibrosis which occurs in Uganda remains unknown but is a distinct possibility

The most important laboratory finding in severe protein deficiency is a decrease in serum proteins particularly in the albumin fraction Normal concentration of total proteins in serum is 6 0 - 8 0 gm/100 ml, of albumin 4 0 to 5 5 gm /100ml The decrease in concentration in protein

FIGURE 1



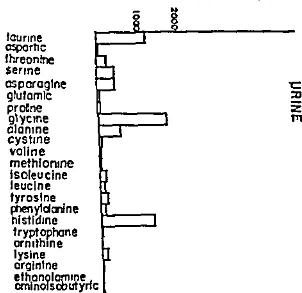


Fig. 1* Concentrations of individual amino acids in plasma of normal adults and daily urinary excretion of free amino acids by normal adult males

* Reprinted from Harrison, H. E., and Harrison, H. C. J.A.M.A. 164, 1572, Aug 1957

not be detected and it is possible to obtain positive bal ance when some labile protein stores are being depleted

Recent studies indicate that tissues enzymes respond to changes in dietary protein It seems likely that measure ment of enzyme activity in tissues may prove useful in *determining the presence and severity of deficiency* and, perhaps, deficiency of specific amino acids The liver would appear to be a good organ for study as changes in enzyme activity of the liver have been found to accom pany variations in exogenous protein intake (17)

Numerous methods for determining the concentration of amino acids in blood and urine are available Tech niques include chemical and microbiologic assay and chromatography using paper or ion exchange columns Amino acid determinations have been of value in detecting metabolic derangements but have been of little assistance *in evaluating over all protein nutrition* The amino acid content of plasma during fasting does not fluctuate significantly despite considerable variation in amounts ingested (32) and does not parallel quantities excreted in the urine due to marked differences in reabsorption of individual amino acids by the renal tubules (33) Diets high in protein are, however, associated with slight in creases in 24 hour excretion of amino acids particularly with respect to histidine Normal plasma levels and pat tern of urinary excretion are given in Fig 1 Excretion can be increased by either of two mechanisms, hyperaminoacidemia or changes in renal tubular absorption Abnormal excretion of amino acids has been reported in advanced liver disease and after radiation injury but not following surgical procedures when nitrogen balance is negative (34)

Diseases associated with aminoaciduria have been re viewed by the Harrisons (33) Specific aminoaciduria of

in reduction of the aminoaciduria in the Fanconi syndrome

Under ordinary dietary conditions, the loss of amino acids in the urine has not been found to be sufficiently great to produce deficiencies The only significant disturbance directly due to excessive excretion of amino acids is the formation of cystine calculi in the urinary tract in cystinuria (33)

From data just discussed, it is evident that estimation of excretion of individual amino acids is a useful procedure in the diagnosis of a number of diseases associated with metabolic abnormalities Such determinations are useful also in clarifying interrelations among these diseases and among vitamins and amino acids

SPECIFIC AMINO ACID DEFICIENCIES

Little is known about specific amino acid deficiencies in man Albanese (36) has suggested that changes in amino acid levels in blood and urine may be useful in detecting certain deficiencies Further investigation will be needed to substantiate this postulate Tryptophan is known to be a precursor of the vitamin niacin, and hence an inadequate dietary supply of tryptophan contributes to the development of niacin deficiency or pellagra (37) Methionine metabolism has been widely investigated in animals but little is known about the application of findings to man Relationships between methionine choline vitamin B_{12} and folic acid have been observed in animals Each of these nutrients participates in some way in the metabolism of methyl groups Such groups are important in the prevention of fatty livers and cirrhosis in animals which are fed diets high in fat or low in protein and low in fat It seems likely that methyl groups are of similar importance in human nutrition

hyperaminoacidemic type occurs in phenylketonuria (phenylpyruvic oligophrenia), an inborn error of metabo lism In this condition, conversion of phenylalanine to tyrosine is defective, phenylalanine levels in plasma are markedly increased and urinary excretion is correspondingly high The aminoaciduria of severe liver damage is due to generalized hyperaminoacidemia but taurine, cy stine, methionine, ethanolamine and β aminobutyric acid are found in larger amounts than in other types of general aminoaciduria

Aminoacidurias of renal origin include a number of con ditions, some due to inborn metabolic errors, some to toxic agents and others to vitamin deficiency states In patients with scurvy and in premature infants, the feeding of high protein diets leads to hydroxyphenyluria The abnormal excretion of hydroxyphenyl derivatives may be prevented by giving ascorbic acid or large amounts of folic acid (35) Renal aminoaciduria has been reported in infants with vitamin D deficiency (33) The excretion of free amino acids in rickets is qualitatively similar to that found in the Fanconi syndrome although less marked The greatest increases in excretion are in threonine, serine and alanine with slight increases in valine, methionine, leucine, iso leucine and phenylalanine The Fanconi syndrome, which is characterized by bony changes of rickets or osteomala cia hypophosphatemia glycosuria and renal aminoacid uria, may be due to an hereditary metabolic abnormality or occur in older children or adults without familial inci dence The fundamental defect appears to be renal tubu lar injury, especially of the systems involving amino acids, glucose and phosphate Treatment of rickets with vitamin D leads to a gradual return of amino acid excretion to normal Administration of large does of vitamin D results

studying many of the syndromes associated with protein deficiency Certain other changes in cirrhosis of the liver which are of nutritional import may be mentioned, although they are not related directly to protein nutrition An increased loss of fat in the stools has been observed that has been postulated to be due to defective formation of bile salts (42) In decompensated alcoholic cirrhosis, serum concentrations of sodium, potassium, calcium and phosphorus have been found to be lower than normal, while pyruvic acid concentration in the blood has been elevated (43) The low calcium and phosphorus levels may have been due to an increase in fecal fat

In hepatic coma, concentrations of pyruvate and α keto glutarate have been found to be high in both blood and spinal fluid Since thiamine administration does not influence these levels, it has been postulated that the liver may be unable to assimilate pyruvic acid to form the carboxylic acids of the Krebs cycle or that a partial deficiency of cocarboxylase may be responsible High blood ammonia concentrations have been observed, also, in hepatic coma (44) It has been suggested that high concentrations of keto acids in hepatic coma may represent a defect in intermediary metabolism due to impaired utilization of ammonia and faulty removal from the blood by the diseased liver

THE KWASHIORKOR SYNDROME

In many areas of the world, infants and young children develop a syndrome of protein malnutrition that is of serious import This condition is designated Kwashiorkor in Africa (38) and Syndrome Policarencial Infantil in Central and South America (45) The primary cause of kwashiorkor is a diet deficient in protein of good quality and the disease appears in the age groups where

PROTEIN NUTRITION AND CIRRHOSIS OF THE LIVER

While the role of nutrition in the pathogenesis of cirrhosis of the liver in man has not been elucidated in its entirety, evidence from many sources suggests a relation ship between a deficient intake of protein and the de velopment of fatty infiltration, cellular necrosis and fi brosis of the liver (38) The dietary history of many patients with cirrhosis indicates a low intake of protein and of B complex vitamins The institution of a diet rich in protein has been followed by improvement in the clinical condition of the patient and in liver function tests Eckhardt and associates (39) found that provision of a diet adequate in protein resulted in a decrease in liver fat and a return of the size and appearance of liver cells to normal

In patients with untreated cirrhosis in whom biopsy specimens showed fatty infiltration of the liver, adminis tration of a large single dose of methionine or choline has been shown to increase phospholipid turnover (40) Studies of Kirsner (41) suggest that in patients with cirrhosis amino acids other than methionine may be metabolized adequately although less efficiently than normal In acute severe hepatitis concentrations of me thionine in plasma are greatly increased A high protein intake is contraindicated under these circumstances and in impending hepatic coma

A detailed discussion of the diagnosis of cirrhosis is not warranted here but it seems pertinent to emphasize the importance of searching for evidence of liver dysfunction in the presence of serious dietary deficiency of protein A palpable liver abnormal liver function tests and histo-logic changes in liver tissue obtained by biopsy will es tablish the presence of liver disease Measurement of enzyme activity in biopsy specimens may prove useful in

studying many of the syndromes associated with protein deficiency Certain other changes in cirrhosis of the liver which are of nutritional import may be mentioned, although they are not related directly to protein nutrition An increased loss of fat in the stools has been observed that has been postulated to be due to defective formation of bile salts (42) In decompensated alcoholic cirrhosis, serum concentrations of sodium, potassium, calcium and phosphorus have been found to be lower than normal, while pyruvic acid concentration in the blood has been elevated (43) The low calcium and phosphorus levels may have been due to an increase in fecal fat

In hepatic coma, concentrations of pyruvate and α keto glutarate have been found to be high in both blood and spinal fluid Since thiamine administration does not influence these levels, it has been postulated that the liver may be unable to assimilate pyruvic acid to form the carboxylic acids of the Krebs cycle or that a partial deficiency of cocarboxylase may be responsible High blood ammonia concentrations have been observed, also, in hepatic coma (44) It has been suggested that high concentrations of keto acids in hepatic coma may represent a defect in intermediary metabolism due to impaired utilization of ammonia and faulty removal from the blood by the diseased liver

THE KWASHIORKOR SYNDROME

In many areas of the world, infants and young children develop a syndrome of protein malnutrition that is of serious import This condition is designated Kwashiorkor in Africa (38) and Syndrome Policarencial Infantil in Central and South America (45) The primary cause of kwashiorkor is a diet deficient in protein of good quality and the disease appears in the age groups where

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A detailed discussion of the diagnosis of cirrhosis is not warranted here but it seems pertinent to emphasize the importance of searching for evidence of liver dysfunction in the presence of serious dietary deficiency of protein A palpable liver, abnormal liver function tests and histologic changes in liver tissue obtained by biopsy will establish the presence of liver disease Measurement of enzyme activity in biopsy specimens may prove useful in

color, and falls out readily In older children, the "flag" sign may be observed when the hair is held up away from the scalp, stripes of normal color and of depigmentation may be noted, presumably signifying periods of dietary improvement and inadequacy, respectively Factors responsible for these changes in the hair have not been elucidated It has been postulated that deficiencies of sulfur containing amino acids or of B complex vitamins may be responsible

Alterations in function of the kidneys and heart have been reported in kwashiorkor Oliguria is frequent and electrocardiographic changes have been observed The latter include diminished amplitude of all deflections and prolongation of the Q-T interval (46)

Laboratory findings in kwashiorkor include anemia which may be normocytic or slightly macrocytic, the bone marrow shows relative hypoplasia of the erythroid series (46) There is a decrease in pancreatic enzymes as determined by duodenal intubation and low levels of serum amylase, esterase, lipase and alkaline phosphatase are observed Serum protein concentration is reduced markedly, especially the albumin fraction Specimens of liver obtained by biopsy show fatty infiltration, cellular necrosis, fibrosis or a combination of these changes Waterlow (47) has found a fall in liver pseudo-cholinesterase paralleling the fall in plasma proteins

Skim milk powder has been found to be effective in the treatment of kwashiorkor and its use has led to marked reduction in mortality Recently, pure casein and amino acid mixtures have been shown to initiate recovery (48) Complete rehabilitation may require many months even though an adequate diet high in protein is administered

Undoubtedly many mild cases of kwashiorkor go unrecognized even in endemic areas, until intercurrent

protein need is greatest Manifestations of this syndrome vary somewhat from one area to another due, in large part, to differences in diet, in some localities, caloric undernutrition and vitamin deficiency exist concomitantly with deficiency of protein Kwashiorkor is extremely rare *in the United States although isolated cases have been* observed

The fundamental signs of kwashiorkor in Africa are retarded growth in the late breast feeding, weaning and post weaning period, alterations in pigmentation of the skin and hair, edema, fatty infiltration, cellular necrosis or fibrosis of the liver and a high mortality unless good dietary protein is provided (38) Atrophy of the acini of the pancreas is considered by several investigators to be a fundamental lesion

In central America deficiency of calories and vitamins often complicate the clinical picture (45) In this area unlike Africa, the incidence of kwashiorkor is relatively high in children more than four years of age and may be seen up to the age of twelve

Other features of kwashiorkor which are commonly encountered include dermatoses, gastrointestinal disturbances such as anorexia, digestive upsets, diarrhea and steatorrhea peevishness and mental apathy, and anemia The skin lesions are multiple in type bizarre in appearance, and have been designated "crazy pavement" dermatosis Hyperpigmentation is frequent, with lesions which resemble pellagra, except for their distribution which is generalized rather than limited to areas exposed to sunlight or trauma Vascular changes hyperkeratinization and secondary infection are often observed The etiology of the skin lesions is uncertain vitamin amino acid, or multiple deficiencies have been implicated The hair becomes "dyspigmented," often assuming a reddish

CARBOHYDRATE NUTRITION

There is no true dietary requirement for carbohydrate since it can be synthesized in the body from either protein or fat Carbohydrate is utilized chiefly as a source of energy and furnishes 50 to 60 per cent of the calories in the average American diet It is more efficient than protein or fat in providing fuel for muscular exercise Carbohydrate has an antiketogenic action in that it inhibits the breakdown of fatty acids in the liver and it has a protein sparing action by decreasing the rate of deamination of amino acids Carbohydrate is essential for normal function of the heart and nervous system, the latter using only glucose to supply energy needs The concentration of glucose in the blood must be maintained above a critical level or serious damage may ensue, particularly to the brain or myocardium The hemostatic mechanisms responsible for maintaining a relatively constand level of blood glucose include enzymatic, nervous and hormonal components (49)

Carbohydrate is stored in the liver and muscles in the form of glycogen the extent of stores varying with the type of diet ingested Glycogen stores are highest when the diet contains large amounts of carbohydrate, intermediate when the diet is high in protein and lowest when the diet is high in fat Diets rich in carbohydrate protect the liver against injury by ensuring adequate storage of glycogen

Carbohydrate has a detoxifying action in the liver, acetyl groups derived from carbohydrate are used in

infection or parasitism precipitates the characteristic syndrome Further investigation should elicit early findings and lead to recognition before the disorder has become advanced

In regions of the world where kwashiorkor is common, a high incidence of chronic liver disease, not only cirrhosis but also primary carcinoma, is observed in adults Relationships of these pathologic changes to chronic protein malnutrition require further investigation

PROTEIN NEEDS FOR REPLETION

In planning nutritional rehabilitation of a patient with protein deficiency, certain findings in studies of protein repletion in animals appear pertinent It has been shown that the utilization rate for a particular essential amino acid for repletion exceeds the rate for maintenance by a factor of 2 to 5 On this basis, the protein needs of depleted patients would be at least double those of normal subjects (17) The severity of protein depletion can be estimated only grossly with present techniques The following data considered together, should prove helpful the amount of weight lost (actually the loss of muscle and other active metabolizing tissue), the extent of the decrease in total circulating plasma protein particularly albumin, and in tissue proteins as reflected by this decrease (see p 39) and the daily loss of protein or nitrogen in urine stools, exudates and effusions It should be remembered also that amino acid requirements for repletion of specific tissue proteins vary according to the structure of the protein and the position it holds in the dynamic state of the body (17)

persons excrete less than 0 1 per cent glucose in the urine, an amount not detectable with the usual clinical laboratory procedures An increase in glucose excretion and an abnormally high concentration of glucose in the blood in the post absorptive state (greater than 130 mg / ml/) is suggestive evidence of diabetes mellitus

The glucose tolerance test assists in establishing the diagnosis, the blood sugar rises to levels above 170-180 mg/100 ml and remains elevated for three hours or more The blood sugar response to oral administration of a large dose of glucose is dependent in part on the previous diet Glucose concentration increases to a greater extent and for a more prolonged period when the diet has been high in fat than when it has been high in protein, the elevation is still less and of shorter duration when a high carbo hydrate diet has been consumed In starvation the glu cose tolerance test is similar to that observed following administration of a diet high in fat, the increase in blood glucose concentration resembles, in degree and duration, that found in diabetes mellitus although the fasting blood sugar level tends to be low

In sprue nutritional macrocyptic anemia and some vitamin B complex deficiency syndromes a flat glucose tolerance test is observed i e glucose concentration rises very little after administration of a large oral dose Administration of folic acid or vitamin B_{12} improves glucose absorption in sprue and nutritional macrocytic anemia in most instances (50)

Many factors influence the absorption of glucose from the intestinal tract These include the food mixture in the intestine the status of the intestinal mucous membrane the function of the endocrine glands particularly the thyroid anterior pituitary and adrenal cortex and, as noted above the intake of vitamins of the B complex Absorption

acetylation of numerous compounds and glycuronic acid, a carbohydrate derivative, combines with phenolic hydroxyl groups This latter reaction may be important in regulation of the metabolism of steroid hormones and in prevention of excessive accumulation of the sex hormones in the body

A number of the coenzymes involved in the degradation and synthesis of carbohydrates are formed from vitamins of the B complex Coenzymes containing thiamine, riboflavin, niacinamide, vitamin B_6 and pantothenic acid have vital roles in intermediate carbohydrate metabolism Accordingly, diets rich in carbohydrate require a generous supply of these vitamins and an inadequate quantity of any one of them will prevent metabolic processes from proceeding normally This information is applied in the diagnosis of deficiency of one of the B vitamins, thiamine in which pyruvic acid an intermediate in the breakdown of glucose accumulates in the blood and tissues (See p 107)

Much has been learned in recent years about the hormonal regulation of carbohydrate metabolism, of the roles of insulin and of the adrenal and pituitary hormones This subject will not be discussed since it belongs largely in the *field of endocrinology rather than nutrition*

Abnormalities of carbohydrate metabolism are usually hormonal rather than nutritional in origin However, changes do occur in starvation (19) and in certain nutritional disorders associated with malabsorption (See p 123)

The simplest tests used in evaluating carbohydrate metabolism are determination of glucose excretion in the urine and estimation of glucose concentration in the blood during fasting and at intervals after the administration of a large dose of glucose, the glucose tolerance test Normal

LIPID NUTRITION

UNTIL recently, few attempts have been made to evaluate lipid nutrition aside from estimation of the extent of body fat stores in relation to obesity Fats have been considered largely as a source of calories, as carriers of the fat soluble vitamins and as contributors to the palatability and satiety value of diets There has been considerable but sporadic interest in cholesterol metabolism and hypercholesterolemic states A few studies have been carried out relative to the essentiality for man of certain polyunsaturated fatty acids which are known to be required in the diet of many animal species (51a) In the past few years, however, evidence has accumulated that suggests a relationship between dietary fat, serum lipid levels and the development of atherosclerosis As a result, extensive research in lipid metabolism has been stimulated and a new area of nutritional diagnosis is being developed

Lipids comprise a wide variety of chemical compounds the most important of which are fatty acids, triglycerides (neutral fat) phospholipids and sterols Triglycerides consist of three fatty acids combined with glycerol There are many types of phospholipids and there are two important sterols cholesterol found in animal tissues and sitosterol in plants

Fatty acids differ in chain length (number of carbon atoms) and in degree of unsaturation (number of double bonds) The polyunsaturated fatty acids, linoleic linolenic and arachidonic constitute the essential fatty acids for

is abnormally rapid in hyperthyroidism and abnormally slow in hypothyroidism, hypopituitarism and adrenal insufficiency The glucose tolerance test is of diabetic type in hyperthyroidism and in hyperfunction of the pituitary gland and adrenal cortex A flat glucose tolerance test is found in hypothyroidism, hypopituitarism and hypofunction of the adrenal cortex

An excessive fall in blood sugar after a meal, especially one high in sugar, is observed not infrequently in persons who are otherwise normal This functional hypoglycemia may be due to the same mechanism as that which appears to be operative in disease of the pituitary or adrenal gland namely, failure of the liver to respond with an increased output of glucose until the blood sugar concentration has decreased to levels lower than normal

viduals and increases with age, but neither the normal nor optimal level is known In this country, Stare (51f) has reported mean cholesterol levels in men and women aged 40-45 years to be 240 and 225 mg per 100 ml respectively There is some evidence that suggests that these levels may be higher than desirable Sixty per cent or more of the cholesterol in blood is esterified, the remainder being present in free form It is thought that esterification occurs preferentially with unsaturated fatty acids

All of the lipids in blood are transported in combination with protein, cholesterol, phospholipid and triglyceride with globulin, unesterified fatty acids with albumin Lipoproteins have been studied with several techniques to effect separation, e g, by electrophoresis ultracentrifugation and Cohn fractionation Accordingly, the major fractions have been designated variously leading to confusion in terminology (51b) When lipoproteins are separated by ultracentrifugation the very low density lipoproteins with Svedberg flotation (S_f) unit values of 10 to 400 correspond in general to the "alpha" lipoproteins separated electrophoretically, lipoproteins of low density, S_f values of 0 to 10 correspond to the "beta" lipoproteins, while the high density lipoproteins include the "alpha$_1$" lipoproteins The albumin unesterified fatty acid complex is of still higher density Chylomicrons which are present only when large amounts of absorbed fat has entered the blood have extremely low density, S_f value about 40 000 units Both high and low density lipoproteins contain protein triglyceride, cholesterol and phospholipid but in varying proportions

It is possible to measure the several moieties which make up the various groups of lipoproteins including their constituent fatty acids Methods are difficult, however and applicable largely in research rather in general diagnosis

animals Presumably they will be found to be essential for man but this has not been demonstrated unequivocally

The optimal level of fat in the diet is not known and since fat may be formed from protein or carbohydrate, no requirement can be formulated Recent evidence suggests that both the amount and type of fat in the diet have an important effect on serum lipid levels and that lipid levels in turn may have an influence on the development of atherosclerosis (51, 52) Diets high in fat increase serum cholesterol and other lipid levels if other conditions remain the same With diets of comparable fat content, serum cholesterol concentrations are lower when the dietary fat contains large amounts of unsaturated fatty acids than when it is made up largely of saturated fatty acids The polyunsaturated or essential fatty acids may be of particular importance in this situation Thus in evaluating lipid nutrition not only should the total fat intake be ascertained but also the type of fatty acids included in the diet

The cholesterol content of the diet does not significantly influence serum cholesterol concentration over a range of intake of 250 to 800 mg daily which corresponds to quantities present in a wide variety of diets (53) Cholesterol is manufactured in amounts of 1 5 to 2 0 gm daily from acetate (54) which in turn can be formed from protein or carbohydrate

SERUM LIPID CONCENTRATIONS

Plasma contains approximately 300 mg of fatty acids per 100 ml 80 per cent of the fatty acids are present as phospholipids or as simple esters of glycerol (triglycerides), 15 per cent are esterified with cholesterol and 5 per cent are unesterified (51b) The blood cholesterol level varies widely among population groups and among indi

diseases associated with hypercholesterolemia such as diabetes mellitus, hypothyroidism and the nephroses Persons who have coronary artery disease have been found to have higher mean levels of serum cholesterol than persons of similar age and sex who have no clinically demonstrable atherosclerosis In spite of the limitations in interpreting serum cholesterol concentration, this measurement gives as much information relative to the possibility of atherosclerotic complications developing as does any other determination currently available

Simple examination of fasting serum for turbidity or milkiness, in conjunction with a cholesterol determination, is also informative (51b) In general, an elevated serum cholesterol level will be associated with an increase in the concentration of low or very low density lipoproteins Marked elevation of cholesterol concentration in clear serum usually reflects an increase in the low density lipoproteins (S_f 0 to 10) and the serum often is deep yellow in color due to the carotene carried by this fraction Lactescence of the serum implies an increase in triglycerides and of the lower density (higher S_f) lipoproteins Idiopathic hyperlipemia is associated with marked turbidity and the bulk of the triglyceride rich lipoproteins may be chylomicrons

Measurement of specific lipoprotein fractions is of assistance in evaluating lipid metabolism in a number of diseases (51b) Xanthomatous biliary cirrhosis may be accompanied by very low concentrations of high density lipoproteins even though serum cholesterol may be abnormally high In untreated diabetic acidosis and glycogen storage disease, the low density lipoproteins are increased In the nephrotic syndrome, the concentration of very low density lipoproteins is often elevated There is a difference in lipoprotein concentrations between men and women

Little is known about the specific functions of the lipo proteins or relationships of one class to another Fred erickson (51b) has stated It appears that the unifying hypothesis of a single parent molecule, such as the chy lomicron, which would simply be shorn of more and more of its triglyceride to become lipoproteins of successively decreasing size and greater density is not tenable for the whole lipoprotein spectrum although it may be true in part

Studies of the mechanism by which blood is cleared of fat indicate that a lipoprotein lipase probably catalyzes the hydrolysis of triglyceride and is responsible for the disappearance of chylomicrons and very low density lipo proteins This enzyme has been isolated from the heart and from adipose tissue It appears to be identical with the clearing factor found in blood after the injection of heparin (51b)

There is evidence that the unesterified fatty acid frac tion of plasma is of considerable significance, presumably it is in this form that fat is transported from depots to other tissues for utilization

In view of the complexities of lipid metabolism it is obvious that evaluation of lipid nutrition will be no easy task A relatively simple biochemical measurement, that of serum cholesterol, has been widely studied in recent years particularly with reference to atherosclerosis The current status of knowledge of relationships between dietary fat, serum lipid levels and atherosclerosis has been summarized in several recent reviews (51, 52)

Determination of serum cholesterol concentration is of value in assessment of lipid nutrition although the normal or ideal level is unknown and there are wide variations among individuals and even in the same person at differ- ent times The incidence of atherosclerosis is increased in

and enzymatic breakdown to fatty acids is unimpaired It has been postulated that the malabsorption may be due to a defective phosphorylating mechanism as a result of deficiency of one or more vitamins of the B complex Since administration of folic acid and vitamin B_1 often improve absorption, these vitamins may be involved Another condition associated with malabsorption of fat is pancreatic fibrosis In this situation, a lessened amount of pancreatic lipase is responsible for failure to hydrolyze fat

The best method for measuring fat absorption is the metabolic balance study in which both dietary intake and fecal excretion of fat are determined In clinical diagnosis, this is seldom feasible Gross and microscopic examination of the stool for fat gives some information if the previous and current dietary intake of fat can be estimated but this is only a rough qualitative test at best

A procedure that has been widely used in studying fat absorption is the vitamin A tolerance test A large dose of vitamin A in an oily medium is administered for example 5000 I U per kilogram of body weight, and blood levels are determined before and at 3 6 9 and 12 hours after the test dose In normal subjects the concentration of vitamin A in blood increases markedly usually five fold or more In patients with malabsorption of fat, only small and delayed increases in serum vitamin A are observed (See Table 6)

The administration of Lipiodol® with measurement of iodine excretion in the urine has been suggested as a procedure for estimation of fat absorption but this test has not proved satisfactory

Estimation of the degree of lipemia after ingestion of a test meal of fat has been used to some extent in studying fat absorption Since chemical analysis of lipids presents serious technical difficulties, determination of plasma tur-

In the age group 15 to 65 the male has higher concentrations of all major low density lipoproteins than the female. Gofman (55) has shown that in patients who have had a myocardial infarction the levels of low density lipoproteins, especially S_f 12-400 classes, are elevated.

Other measurements of lipid nutrition include chylomicron counts and determination of phospholipid concentration in blood and of the phospholipid cholesterol ratio. Accurate chylomicron counts are difficult to obtain and the interpretation of findings is uncertain. Elevated or prolonged chylomicronemia has been suggested as a possible contributing factor to the development of atherosclerosis but data are few. The normal phospholipid concentration in serum is in the neighborhood of 220 mg per 100 ml and increases with age as does cholesterol concentration. A decrease in the phospholipid cholesterol ratio has been considered an undesirable finding. The concentration of polyunsaturated fatty acids in serum may be measured but methods are difficult and as yet no standards of normalcy are available. It is anticipated that the great attention currently being directed to lipid metabolism will evolve new tests and more accurate methods of evaluating lipid nutrition in the near future.

ABSORPTION OF LIPIDS

Abnormalities in fat absorption present another problem frequently encountered in clinical nutrition. Bile salts have an important role in the emulsifying system which affects absorption of lipids. Impaired absorption of fat is observed when bile is absent from the intestinal tract, as in obstructive jaundice, although the hydrolysis of fat to fatty acids and glycerol by pancreatic lipase proceeds normally. Fat is poorly absorbed in sprue, idiopathic steatorrhea and the celiac syndrome although bile is available

manner as described for triolein (56) Most patients who have diseases of the pancreas will have significant impairment of absorption of neutral fat and normal absorption of fatty acid Subtotal gastric resection has been found to result in impaired neutral fat absorption in approximately half of the paitents studied (56)

KETOSIS

Ketosis should be mentioned briefly since it is occasionally a nutritional problem Fat is used for energy continuously to some extent, but when there is a shortage of carbohydrate, fat is needed for this purpose in increased amounts Fat is degraded by rapid fragmentation of long chain fatty acids to form 2-carbon and occasionally 4-carbon units Two-carbon units may enter the tricarboxylic acid cycle, may be synthesized to fatty acids or cholesterol, or may condense to form aceto-acetic acid Aceto-acetic acid may be used in the tissues but is not broken down in the liver The formation of this compound is greatly increased in diabetes mellitus and in starvation When the concentration of aceto-acetic acid in the blood reaches 20 mg per 100 ml ketonuria results Some of the aceto-acetic acid is converted to β hydroxy butyric acid and acetone Accumulation of these substances results in acidosis Diagnosis of ketosis is relatively easy as simple tests are available for measurement of ketone bodies in urine and in blood

LIPIDS AND LIVER DISEASE

The normal liver contains about 4 per cent fat, the majority of which is phospholipid, the remainder being glycerides and cholesterol In a number of pathologic conditions lipids accumulate in the liver cells and this accumulation is often followed by fibrosis and cirrhosis

bidity or chylomicron counts have been advocated to measure lipemia The latter method is unsatisfactory due to the many variables that influence findings Estimation of plasma turbidity is a simple and informative test which merits further investigation

Recently, lipids labelled with I^{131} have become available for studies of intestinal absorption (56, 57) Triolein and oleic acid labelled with I^{131} are proving most useful in investigating malabsorption syndromes and in differentiating between impairment of digestion and impairment of absorption of fat A test meal of I^{131} triolein is administered in the fasting state and the radioactivity of blood samples is measured at the 4th, 5th and 6th hours thereafter (56) The radioactivity of the total stool passed during the 48 hour period after the meal may be measured also The test meal consist of 25 μc I^{131} triolein 0 5 cc peanut oil per kg body weight, an equal amount of water, 2 cc of Tween 80® and 20 gm of barium sulfate The last ingredient is needed to permit checking the emptying time of the stomach which would influence findings if delayed Fecal excretion correlates well with fat balance studies (58) I^{131} levels in whole blood at the 4th, 5th and 6th hours are indicative of absorption in most instances Normal individuals generally excrete less than 2% of the administered dose of radioacivity in the stools in the 48 hour collection Patients with sprue and celiac disease will have a flat blood curve and high radioactivity in the feces

Abnormalities of fat digestion may be differentiated from those of absorption by administration of a test meal of I^{131}-labeled oleic acid in addition to the test meal with I^{131}-labeled triolein Oleic acid 25 μc is given in a gelatine capsule together with three capsules of barium sulfate and radioactivity in blood determined in the same

MINERAL NUTRITION

Most of the 14 minerals which appear to be essential in human nutrition are widely distributed in foods and for many of them there is little danger that dietary deficiency will occur In a number of pathologic states, however, abnormalities of mineral nutrition develop which require diagnosis and therapy The essential minerals are sodium potassium, chlorine calcium, phosphorus sulfur, magnesium, iron copper, iodine, maganese, cobalt, zinc and molybdenum Until recently, mineral metabolism has been a somewhat neglected field of study, yet minerals, like vitamins have many vital physiologic functions including important roles in enzyme systems

WATER AND ELECTROLYTES

Disturbances of water and electrolyte metabolism are extremely common and important in clinical medicine Our understanding in this field has been increased greatly through the use of isotopic techniques and by investigations of the role of the endocrine glands in water and electrolyte metabolism The method of flame photometry for estimation of sodium and potassium likewise has made a distinct contribution to clinical investigation Only a brief résumé of knowledge in this field, with particular emphasis on nutritional aspects, can be undertaken in this discussion A recent symposium gives many interesting details of some of the newer concepts and their application to medical problems (61)

For centuries water has been recognized as indispen-

Fatty livers have been produced in experimental animals by diets high in fat and by diets low in protein and low in fat Deficiency of choline or methionine appears to be related to the accumulation of lipid in these situations (60) Abundant evidence suggests that cirrhosis of the liver in man is often due to dietary deficiency Administration of choline has been shown to result in a decrease in liver fat in fatty alcoholic cirrhosis (39), both choline and methionine have been found to increase the rate of phospholipid turnover (40) The value of diets high in protein in the prevention and treatment of experimental cirrhosis is well documented, evidence strongly suggests that this is the case in man

LIPIDS AND GALLBLADDER DISEASE

Lipids have long been implicated in disease of the gallbladder particularly in the pathogenesis of cholelithiasis Gallbladder disease occurs with increased frequency in hypercholesterolemic states There is little precise information however, on the metabolic abnormalities which are responsible for the formation of gallstones Bile contains cholesterol and cholesterol is metabolized to bile acids The gallbladder wall can absorb lipids and cholesterol deposits are common in the wall and lumen of the gallbladder, increasing with advancing age Aside from these few facts, little is known of the role of cholesterol in the production of cholelithiasis The current extensive investigation of lipid metabolism should elucidate this problem

organ in the hypothalamus Perhaps a deficit in volume in some key portion of the body fluids may promote secretion also Painful and disagreeable stimuli increase secretion

The normal adult kidney can excrete the catabolites formed in 24 hours in as little as 500 ml of urine In the infant, the ability to concentrate urine is limited, the metabolic rate is higher, more metabolites per unit of body size must be excreted and insensible loss of water from the skin is greater than in the adult As a result, depletion of body water can occur more rapidly and be of more serious consequence

The total amount of water in the body comprises about 50 to 55 per cent of total body weight, the volume of extracellular fluid amounts to approximately 23 per cent, the plasma volume to about 5 per cent of body weight. Methods for measuring the fluid content of the body and its compartments consist chiefly of dilution techniques many of which employ radioactive isotopes Details of a number of these procedures and findings in certain disease states are given in a recent report by Moore and associates (61a)

Water Depletion

The syndrome of water depletion was studied in normal subjects by Black, McCance and Young (62) The initial and most prominent symptom was intense thirst the mouth became dry and there was difficulty in swallowing Weakness oliguria and loss of weight in proportion to water deficit were observed Other findings included a change in temperament, confusion and hallucinations Plasma volume decreased slightly serum sodium increased and serum potassium decreased Severe dehydration resulted in prostration peripheral circulatory collapse, anemia, azotemia and serious electrolyte disturbances

sable and man can live for only short periods without it. The daily requirement is about 1 ml. for each calorie of food or approximately 2.5 liters for the normal adult living in a temperate climate. This water is supplied approximately as follows: 1200 ml. as liquids, 1000 ml. from the water in solid foods and 300 ml. from the water produced by oxidation. When water balance is being maintained, the loss is likewise about 2.5 liters of which approximately 1500 ml. is excreted by the kidneys, 500 ml. by the skin as insensible perspiration, 500 ml. in the expired air and 100 ml. in the stool. The minimal intake of water which will meet requirements during fasting, if activity is limited, is 0.8 liter daily which represents about 50 per cent of the need. The remainder is furnished by oxidation and release of cellular water. Water requirement may be increased markedly in conditions associated with profuse sweating, vomiting, diarrhea or polyuria.

Fluid is continually being exchanged between the various compartments of the body and balance is maintained by a number of regulatory mechanisms. Water which is excreted into the intestinal tract each day may amount to as much as 8 liters of which all but 100 ml. is reabsorbed under normal conditions. Normally, no electrolyte is lost in the expired air or in insensible perspiration and little in the intestinal discharge. Accordingly, the kidney is primarily responsible for water and electrolyte excretion and for maintaining the constancy of the body content of these materials. *Adrenal cortical hormones and the antidiuretic* hormone of the pituitary play important roles in the regulatory mechanism (61b). The primary action of the antidiuretic hormone (A.D.H.) is to decrease renal excretion of water by increasing reabsorption from the kidney tubules. The stimulus for A.D.H. secretion is an increase in the osmotic pressure of the fluid bathing a receptor

renal ischemia, hypotension and peripheral circulatory failure Oliguria and water retention may follow trauma and perhaps other forms of stress The surgical patient is liable to water retention and intoxication if an excessive amount of sodium free water is administered It has been suggested that anuric patients metabolize large amounts of fat and that this endogenously produced water increases body water even if external water and electrolyte balance remain constant Some surgical patients likewise metabolize considerable amounts of fat The majority of cases of water intoxication result when excessive fluids are given parenterally or per rectum, occasionaly from oral intake

The clinical symptoms of acute water intoxication, according to Wynn (61c), usually begin suddenly with mental disturbances Strange behavior, loss of attention, confusion, staring aphasia, incoordination and sleepiness are interspersed with periods of violent behavior, shouting delirium and extreme muscular weakness" Subsequently, convulsions and coma are observed In cases of insidious onset, lethargy, prostration, muscle weakness, sleepiness, apathy and disorientation are prominent findings Occasionally there is anorexia, nausea and vomiting Signs of water intoxication are largely the reverse of those of sodium depletion There is gain in weight, normal tissue turgor and elasticity normal tension of the eyeballs warm moist skin, normal pulse and normal or slightly elevated blood pressure Muscle strength is reduced In coma, plantar reflexes are extensor in type

Laboratory findings include reduction of hemoglobin and serum protein concentration reflecting the increase in extracellular fluid and blood volume An increase in red cell volume is indicated by a decrease in mean corpuscular hemoglobin concentration Serum sodium and

Dehydration accompanying disease shows many of these findings in conjunction with the primary abnormalities of the pathologic state Acute dehydration may result from excessive sweating an increase in pulmonary or renal water loss, from vomiting fistulae or diarrhea The daily loss may amount to as much as 14 liters in sweat or urine and 8 liters from the gastrointestinal tract In such situations, total body water is reduced but the percentile charge is not great, an acute loss of 7000 ml may result in only a 5 to 7 per cent decrease in total body water However, severe clinical effects ensue Careful measurement of changes in body weight is more useful in detecting the extent of acute water depletion and in following rehydration than the more complicated estimations of body water Determination of the volume of packed erythrocytes, of plasma protein concentration or specific gravity of plasma are of assistance in following the course of dehydrated patients

Water Intoxication

Water intoxication is a term which has been used in the past to describe a syndrome in which water is retained in the body in excess of electrolytes Severe cases are uncommon but significant dilution of body fluids by excess water is frequently observed and also frequently misdiagnosed Actually there are several syndromes to which the above definition might apply, in all of which serum hypotonicity is characteristic These include 1) water retention 2) primary sodium depletion and 3) symptomless hypotonicity or asymptomatic hyponatremia in which the cause is unknown (61c) Primary water retention will be discussed here

Many clinical states may be associated with a reduced ability to excrete water, e g organic renal disease, reflex

carbonate, protein and small amounts of organic acids The pH is regulated in large part by the relative amounts of chloride and bicarbonate The chlorides of the blood constitute about two thirds of the anions, the normal concentration being 104 mEq/l of serum

Recent studies indicate that bone functions as an electrolyte reservoir (61e) Skeletal sodium, which comprises 46% of the total body sodium, undoubtedly plays a role in the sodium economy of the body since some 6 to 13% of this sodium can be mobilized in the adult in response to various stimuli (61d) In animals, a loss of bone sodium has been demonstrated with low sodium diets, in hyperchloremic acidosis, after mercurial diuresis and following adrenalectomy Presumably, similar losses may occur in man under comparable conditions In view of this, total deficits of sodium may be greater than those found by the usual methods of calculation

Sodium plays a role either alone or in conjunction with other extracellular ions, in the conduction of nerve impulses and in muscle contractility (64) Sodium metabolism is associated closely with that of water, although the mechanisms regulating excretion of these substances are not the same These mechanisms maintain the concentration and amount of sodium and water in the body relatively constant within wide ranges of intake

Sodium is excreted in the urine sweat and feces urinary excretion being of greatest importance Losses in sweat are dependent upon the environmental temperature humidity and body heat In the unacclimatized person the salt content of sweat may be 2 to 3 gm per liter whereas after acclimatization sweat will contain only about 0 5 gm per liter Losses of sodium in the stool are small regardless of intake in the absence of diarrhea, since the lower small intestine and colon absorb large amounts The

chloride are reduced, serum potassium is low or normal Serum bicarbonate is moderately reduced and blood urea nitrogen is usually low unless anuria has been a feature of the condition The sodium and chloride concentration of the urine may be quite high despite the low serum concentration

SODIUM AND CHLORIDE

It has been customary to discuss the body requirements of sodium and chloride together In view of current knowledge, it would seem desirable to discuss requirement of sodium separately, as well as in terms of salt The minimum need of sodium is not definitely known but patients have been maintained on diets which furnished 200 to 300 mg daily for long periods without apparent ill effects The usual intake of sodium chloride (salt) by adults in the United States is 7 to 15 gm daily, far more than minimum requirement (4a) This large supply will amply fulfill needs except under conditions of profuse sweating or severe diarrhea or in certain endocrine and metabolic disturbances

Sodium constitutes the largest fraction of the total base of the blood plasma and extracellular fluids, the normal concentration being 140 mEq/l The total exchangeable sodium in the body, as determined by dilution techniques using radio-sodium, is about 2500 mEq or 41 mEq/kg of body weight *Sodium is associated chiefly with chloride* and bicarbonate ions and functions with them to maintain the osmotic pressure and ionic equilibrium of the body fluids and tissues (63) When osmotic equilibrium is disturbed the functional capacity and viability of the cells may be seriously affected

Cations in the blood other than sodium are calcium, potassium and magnesium anions include chloride, bi

The loss of sodium in association with chronic nephritis and certain types of acidosis, for example, diabetic acidosis, has long been appreciated

Excessive retention of sodium is observed in many pathologic conditions including cardiac failure nephritis, nephrosis, cirrhosis of the liver and hyperfunction of the adrenal cortex A primary increase in secretion of aldosterone is observed in certain adrenal tumors while a secondary increase in secretion of this hormone has been demonstrated in the other diseases mentioned above in which sodium retention is common (61i)

The diagnosis of sodium depletion is dependent on appreciation of the situations in which it is likely to occur as well as on clinical and laboratory findings The syndrome is gradual in onset with weakness, lassitude, apathy, and anorexia as early manifestations (65) Postural faintness and restlessness with anxiety may be observed It is noteworthy that thirst, a prominent finding in water depletion, is absent Nausea, vomiting and muscle cramps are noted as the depletion progresses The patient appears haggard tissue turgor and elasticity are decreased and there is loss of weight The blood pressure falls, the pulse pressure is low the limbs are pale and cold, and the pulse is rapid Peripheral circulatory collapse is the mode of death The concentrations of sodium and chloride in the serum are decreased and excretion of these substances in the urine is very low or absent, except in Addison s or renal disease Plasma volume is decreased and as a consequence, levels of serum protein and hemoglobin and the volume of packed erythrocytes are increased Blood urea nitrogen is elevated serum potassium may be increased and serum bicarbonate decreased

Sodium depletion must be differentiated from other syndromes in which hyponatremia is a finding Causes of

urinary excretion of sodium is controlled principally by the renal tubules which reabsorb sodium according to bodily need, glomerular filtration influences loss to a certain extent In the normal adult who ingests an average diet, approximately 100 mEq of sodium is excreted in the urine in 24 hours In view of the magnitude of glomerular filtration, this means that about 99 6% of the sodium presented to the tubules has been reabsorbed (4) When dietary sodium is markedly restricted for several days, almost no sodium is lost in the urine The regulatory mechanism for tubular reabsorption of sodium is controlled in large measure by hormones of the adrenal gland Recent evidence suggests that aldosterone, the recently isolated adrenal hormone, has a major role in salt and water homeostasis The activity of aldosterone is analagous to that of desoxycorticosterone in its effect on renal sodium and potassium excretion but is about 30 times as great According to Bartter (61i) secretion of this hormone is controlled by a function of extracellular fluid volume, a function of potassium ions and, less importantly, adrenocorticotropic hormones

Sodium Depletion and Retention

Sodium metabolism is deranged in many disease states Depletion may occur in subjects receiving diets seriously restricted in sodium, such as those used in the therapy of hypertension or in the control of chronic, extensive edema Sodium deficiency may follow prolonged vomiting diarrhea, profuse sweating exudation of fluid from burned or otherwise injured areas and profound diuresis particularly when low sodium diets have been administered In adrenal insufficiency large amounts of sodium are lost in the urine and much of the symptomatology of Addison s disease may be attributable to sodium depletion

The prognosis is poor unless these is a response to adequate nutritional intake

A number of these patients with chronic disease may have a defect similar to that noted in starvation by Moore and associates (61a) In starvation, total body water expressed as per cent of actual body weight is normal, or nearly so as a result of the balance between marked reduction in intracellular water and marked increase in extracellular fluid The total exchangeable sodium and chloride are very high, while total exchangeable potassium is low in relation to weight Low serum sodium and slightly high serum potassium concentration are observed, the depression in serum sodium representing not dehydration but relative overhydration Moore suggests that these changes may be explained on the basis of insufficient available energy Enery is required for exclusion of sodium from the cell and retention of potassium within the cell and for maintenance of isotonicity of extracellular fluid by the renal tubule These mechanisms may break down in the absence of sufficient energy If this explanation is correct and applicable to certain patients with chronic disease and hyponatremia, the fundamental need of this group of patients may be for energy

It is obvious from the above that accurate diagnosis of the status of sodium metabolism is not simple and that reliance cannot be placed on any single clinical sign or laboratory test The whole picture must be carefully evaluated At times, the more complicated techniques for studying body composition must be applied for clear definition of the situation

Combined Water and Salt Depletion

Combined water and salt depletion is a syndrome commonly encountered in clinical medicine Findings are

hyponatremia other than sodium depletion include depletion of potassium, primary water retention and, possibly, *intracellular hypo osmolarity* due to a change in the state of intracellular anions (61f) The signs of primary water retention have been described (p 67) while those of potassium depletion wil be considered subsequently (p 76)

Hyponatremia may be observed in many chronic, serious illnesses and may develop in the presence of a normal, low, or high total body sodium Clinical assessment of the probable level of body sodium is of primary importance for institution of proper therapy Edelman (61f), from a consideration of data compiled from the literature, suggested that demonstratable edema is a reliable guide to the quantity of sodium in the body Total body sodium was found to be increased by essentially the same amount in edematous subjects with cardiac, hepatic or renal disease who were hyponatremic as in those who were eunatremic Conversely, when total body sodium was decreased dehydration rather than edema accompanied hyponatremia However findings obtained by Moore and associates (61a) in studies of starvation show that total body sodium may be high in the absence of edema This may be true in other hyponatremic states

A type of hyponatremia often seen in patients with chronic illness has been designated asymptomatic hyponatremia by Wynn (61c) who has pointed out that this condition is unaffected by treatment with salt and not corrected by water restriction It may possible be due to a primary lowering of intracellular osmotic pressure Patients with asymptomatic hyponatremia have no findings relative to the low level of serum sodium per se They exhibit tissue wasting progressive loss of weight, normal pulse and blood pressure and usually, a decrease in hemoglobin, volume of packed erythrocytes and serum proteins

amount may be harmful if there is renal damage or adrenal insufficiency

Potassium is the principal cation of the cells, the concentration in extracellular fluids amounting to only a small per cent of the intracellular concentration In the normal adult, the average level of potassium in serum is 4 2 mEq/l in the cells, 112mEq/l (66) Total exchangeable potassium has been found to be 47 mEq/kg of body weight in the male, 40 mEq/kg in the female (61a)

The important role of potassium in metabolism is indicated by the close relationship between cell growth and potassium accumulation and cell breakdown and potassium loss Potassium is closely associated with protein and glycogen and functions in the cells in conjunction with phosphate chloride and bicarbonate The excitability of nerve tissue the transmission of nerve impulses and the contractility of all types of muscles are influenced profoundly by potassium concentration Paralysis of striated muscle is observed when the serum concentration is less than 2 to 2 5 mEq/l Smooth muscle and cardiac muscle, likewise, are affected by potassium deficiency Potassium is involved in a number of enzyme reactions According to Greisheimer (67) the transport of potassium across cell boundaries against existing ionic concentration gradients seems to be linked with the carbohydrate phosphorylation cycle

The kidney is largely responsible for maintaining a balance between the intake and output of potassium in a manner which resembles that for sodium except that during fasting or after tissue damage potassium is released from the cells and excreted in the urine Potassium leaves the cells with nitrogen in the ratio of about 2 7 mEq potassium per gram of nitrogen Schwartz (68) found that potassium excretion is increased under the following con-

those of both water and salt deficiency anorexia, weakness, nausea, vomiting, muscle cramps and peripheral circulatory collapse (signs of sodium deficiency), thirst and oliguria (signs of water deficiency) Heat cramps, which occur in persons working in very hot environments, are an example of this syndrome If only water is ingested, the severity of symptoms is increased

Hypernatremia

Hypernatremia appears to be relatively uncommon as judged by the limited number of publications on this subject In a recent review Knowles (61g) cites the following causes 1) deficient intake of water 2) excessive output of water due to a) solute diuresis of urea or glucose b) uncontrolled diabetes insipidus, c) gastroenteritis or d) hyperventilation, and 3) unclassified Hypernatremia signifies a serum sodium concentration greater than 150 mEq/l It seems likely that a primary water deficiency precedes and initiates the increase in serum sodium concentration in most instances The condition is found most often in elderly patients in whom water intake has been limited or in subjects undergoing solute diuresis from urea or glucose Unless hypernatremia is severe, there are few or no abnormal symptoms or signs In severe cases, coma and bizarre neurologic findings may be observed

POTASSIUM

Potassium is abundant in both plant and animal tissues and primary dietary deficiency is not observed However, potassium depletion is encountered frequently in clinical medicine secondary to a number of pathologic states The minimal daily requirement of potassium is not known but presumably is similar to that of sodium Ingestion of excessive amounts of potassium leads to toxicity Normal persons can take 6 gm daily without danger but this

1 to 3 mEq per 100 calories metabolized, usually 20 to 30 mEq per square meter of body surface in 24 hours (69)

The clinical features of potassium deficiency are dependent on decreased muscular irritability and disturbances of conduction and contractility of the heart muscle Lassitude and general muscular weakness is followed by flaccid paralysis, lethargy and, at times, coma Decreased tone of the smooth muscles produces gastric and intestinal distention, nausea, vomiting and paralytic ileus Cardiac dilation, hypertension congestive heart failure and cardiac arrest may ensue Weakness of the respiratory muscles may be observed Death may be the result of cardiac or respiratory failure or paralytic ileus The paralysis of muscles, both smooth and skeletal, appears to be due to failure of myoneural conduction The electrocardiogram often shows flat or inverted T-waves, prominent U waves, prolongation of the Q T interval and RS T segment depression

Estimation of serum concentration of potassium is useful in evaluating the status of potassium nutrition if findings are interpreted in the light of certain basic considerations Serum concentration of potassium reflects changes in serum pH and in concentration of potassium in cells (69) Scribner and Burnell (61h) suggest that potassium deficiency and excess be defined in terms of a ratio (Kr) between the total potassium content and the total potassium capacity of the body The latter means "the sum total of all anions and other chemical groups outside the extracellular space capable of holding or binding potassium ions" Potassium depletion represents a decrease in Kr, i e in the content-capacity ratio potassium excess, an increase in this ratio Interpretation of serum potassium concentration requires consideration of factors which can alter concentration independently of Kr The most

ditions when serum potassium concentration increases, in both acidosis and alkalosis, by administration of desoxy corticosterone, aldosterone, corticosterone, other corticoids or adrenocorticotropic hormone, or by activation of the adrenal cortex Urine with a high level of sodium is usually high in potassium as well The mercurial diuretics produce alkalosis that may or may not be accompanied by potassium deficit In renal failure with oliguria, or when shock and dehydration are present, potassium may be retained and toxic levels may ensue If urine volume is high, potassium excretion is usually maintained even in advanced renal insufficiency

Moderate amounts of potassium are lost in the stools, about 2 millimoles per day being excreted by healthy infants (69) *In infantile diarrhea, potassium loss in the* stools may amount to 17 millimoles per day

Potassium Deficiency

Potassium deficiency is likely to develop in acidosis and alkalosis and in conditions in which tissues are broken down with resultant loss of potassium in the urine Such conditions include starvation, infections tumors diabetes mellitus and stress situations such as trauma or operative procedures Potassium excretion may be increased by altered renal tubular function in alkalosis Also, potassium deficiency alters renal function so that alkalosis appears or persists Potassium deficiency may be induced by administration of diuretics and of adrenal cortical hormones Loss of potassium in gastrointestinal secretions through diarrhea or vomiting may lead to depletion Intravenous alimentation with solutions free of potassium may also result in deficiency The expenditure of potassium under *conditions of parenteral feeding varies from*

preventing serious deficiency from developing Patients with alkalosis and hypokalemia, also, develop symptoms readily since alkalosis increases the tendency to transfer potassium from extracellular to intracellular fluids In non diabetic acidosis with potassium deficiency, hypokalemia develops more slowly due in part to retardation in transfer of potassium into the cells by the acidosis and to higher initial serum potassium concentration in most instances

Hyperkalemia

Potassium excess and an increase in serum potassium is less common than hypokalemia It is encountered most often in advanced renal disease with oliguria or when renal function is impaired by shock or dehydration It is also seen in adrenal insufficiency or it may be due to the injudicious use of potassium salts Clinical findings in hyperkalemia include mental confusion, weakness, numbness and tingling of the extremities, pallor, cold skin, disturbances in cardiac rhythm and peripheral vascular collapse A flaccid paralysis of skeletal muscle has been observed in advanced renal failure when serum concentration of potassium was high resembling the paralysis seen in potassium deficiency (69) Electrocardiographic changes may appear at serum potassium concentrations above 6 5 mEq/l and abnormalities roughly parallel the degree of potassium increase There is alteration and peaking of the T waves and prolongation of the QRS and PR intervals Finally auricular standstill and delay in intraventricular conduction may occur ending ultimately in total arryhthmia and cardiac arrest

CALCIUM

In spite of extensive investigation of calcium metabolism the most satisfactory level of calcium intake for growth or for maintenance in adult life is unknown and

notable factor is change in extracellular pH In severe alkalosis, serum potassium concentration may be low with an essentially normal content capacity ratio, i e even if cell potassium is normal Serum concentration is especially low when cellular potassium is decreased In alkalosis serum potassium concentration is not likely to be high unless renal function is impaired and cell potassium is relatively normal (69)

In severe acidosis, serum potassium concentration may be high with a normal Kr Concentration may be either normal or high despite cellular defects In fact, a normal *serum potassium concentration in acidosis reflects a mod*erate potassium depletion while a low serum concentration reflects a *profound depletion* Scribner and Burnell (61h) point out that water depletion, changes in the size of the extracellular space and changes in renal function do not cause significant changes in serum potassium concentration which do not reflect Kr Accordingly, they state that in the majority of clinical situations, the serum potassium concentration interpreted in the light of extracellular pH will reflect Kr accurately and, therefore, the potassium needs of patients

*Diabetic coma may be used to illustrate the above prin*ciples Acidosis causes an initial hyperkalemia The magnitude of potassium depletion can be estimated by the severity of the acidosis and the serum potassium concentration When the initial serum potassium concentration is normal or low initial potassium depletion has been moderate or marked After administration of insulin glycogen is deposited and potassium is drawn into the cells Symptoms of deficiency may develop rapidly with restoration of metabolism if deficits have been marked (69) Appreciation of the magnitude of initial depletion and institution of proper therapy is of great importance in

cent is in ionized form, the remainder being bound to protein and varying with the concentration of serum proteins The ionized fraction is responsible for the prevention of tetany Mechanisms for the maintenance of serum calcium are complicated and are dependent upon calcification and decalcification of bone as well as on dietary calcium (63) The parathyroid hormone and vitamin D have dominant roles but the sex hormones, the kidney and the acid base balance of the body are also concerned Relationships between calcium, phosphorus and vitamin D and changes which are observed in rickets are discussed under vitamin D nutrition (p 140)

Calcium excretion varies widely in normal subjects at any given level of intake Excretion is influenced by the calcium intake skeletal size acid base balance and "endogenous factors" which include several of the body hormones (70)

Calcium Deficiency

There is a real need for the development of procedures for evaluating calcium nutrition and detecting deficiency at any early stage Diagnosis at present is dependent upon the appearance of the characteristic clinical picture of tetany which is manifested by carpopedal spasm and, at times convulsive seizures Laryngospasm may occur particularly in children Paresthesias of the hands feet and lips are common Trousseau s and Chvostek s signs are positive The concentration of calcium in serum decreases to low levels, usually to less than 4 m Eq/l

Tetany is observed frequently in association with rickets and osteomalacia and is encountered occasionally in sprue and other steatorrheas "Hunger osteomalacia" which is observed in some subjects during starvation may be due in part to deficiency of calcium as well as of protein

there are no methods available for accurate appraisal of the status of calcium nutrition

Calcium serves as a structural component of bones and teeth which contain 99 per cent of the calcium in the body *The small portion of calcium in serum and soft* tissues exists partly in ionized form and is concerned in neuromuscular excitability, the blood clotting mechanism, and membrane permeability It is known that certain enzymes are activated by calcium At least part of the calcium in the skeleton is available to maintain the level in blood and other tissues when dietary supply is limited The recommended dietary allowances for calcium (Table 3) are based largely on balance studies with their inherent defects and difficulties *in interpretation* Such studies do not indicate the distribution of calcium in the body or the extent of storage Calcium balance tends to reflect pre vious dietary intake and there is evidence of adaptation to low levels of intake

It is known that the ability to utilize calcium from in gested food varies greatly among individuals and that numerous exogenous and endogenous factors influence absorption and excretion Utilization is usually in the neighborhood of 20 to 30 per cent but may be greater in children who are deficient in calcium Absorption is in fluenced by the relative and absolute levels of calcium and phosphorus in the diet ratios between 1 1 and 2 1 being optimal during growth Absorption is facilitated by normal gastric acidity, enhanced by vitamin D and in creased by protein lactose and citrates in the diet Ab-sorption is decreased by the presence of phytates, oxalates and fatty acids in foods due to the formation of insoluble calcium salts

The normal concentration of calcium in the blood is 9 to 11 5 mg per 100 ml (4 5-6 0 mEq/1) of which 50 60 per

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The osteoporosis of aging is considered to represent a failure of bone matrix formation rather than calcium deficiency Therapy with calcium is not efficacious although administration of sex hormones may be beneficial

Hypercalcemia and metastatic calcification of tissue does not occur as a result of excessive dietary intake alone but is dependent on excessive administration of vitamin D or some metabolic abnormality such as hyperparathyroidism

PHOSPHORUS

The abundant supply of phosphorus in foods almost precludes the possibility of dietary deficiency occurring in man The daily allowance should probably be about equal to that of calcium for children and for women during pregnancy, perhaps 1 5 times that of calcium for other adults (4a) Phosphorus is distributed in the body as follows about 80 per cent in bones and teeth, 10 per cent in combination with proteins lipids carbohydrates and other organic compounds in muscles and the remainder throughout the body in organic combination (63) The deposition and release of phosphorus from bones is dependent on the same mechanisms that affect calcium

Phosphorus has a vital role in many metabolic processes phosphorus compounds are essential in fat and carbohydrate metabolism and are involved in muscle contraction and in energy transfer systems Phosphorylation is essential for absorption of certain nutrients Phosphates of extracellular fluid participate in acid base regulation and phosphate is the chief inorganic ion of intracellular fluid The normal inorganic phosphate concentration in blood is 2 to 4 5 mg/100 ml (1 2-3 0 mEq/l) in adults 3 to 5 mg/100 ml (2 5 4 5 mEq/l) in children

Phosphorus metabolism like that of calcium is disturbed in rickets osteomalacia and diseases of the thyroid

and parathyroid glands The metabolism of this mineral is also influenced by the steroid hormones In rickets, urinary excretion of phosphorus is increased This also occurs in the Fanconi syndrome apparently due to a renal lesion which prevents reabsorption of phosphorus from the tubules (p 42) In "resistant rickets," studies with radioactive phosphorus have shown phosphorus absorption to be normal Mechanisms responsible for this syndrome have not been determined, endocrine imbalance, abnormal renal function or metabolic abnormalities have been suggested

MAGNESIUM

Magnesium is undoubtedly required for growth and maintenance but little is known about the quantitative need in man Diets containing 0.25 to 0 3 mg of magnesium daily, have maintained adults in balance (71) The body contains over 20 gm of magnesium of which more than half is found in bone in combination with calcium and phosphorus The remainder is present in soft tissues largely within the cells where it functions as a catalyst in a number of enzymatic reactions

Magnesium deficiency has been observed in several species of animals, neuromuscular abnormalities and renal damage being prominent findings Deficiency in man is not clearly defined although low levels of serum magnesium have been reported in many pathological conditions Low magnesium concentration has been found in association with muscle twitching and convulsions but may be present without any characteristic symptoms The normal value for serum magnesium varies with the method of determination Flink (71) reports a mean value of 1 91 ± 0 2 mEq/1 by the molybdivanadate method and 2 27 ± 0 26 mEq/1 by the titan yellow method Serum magnesium does not always reflect body stores of this

substance just as serum potassium concentration may not be indicative of body content

Depletion of body magnesium has been demonstrated in diabetic acidosis Flink and associates (71) reported magnesium deficiency in chronic alcoholism and in certain other chronic debilitating illnesses Gross muscle tremor and delirium were common findings, muscular twitching, choreiform and athetoid movements and convulsions were encountered at times Serum magnesium concentration was low in most instances Administration of a magnesium salt appeared beneficial in a number of subjects who had the above findings Response was dramatic in some instances but required several days in others

The authors believe that the major manifestations of magnesium deficiency are related to cellular deficit The pathogenesis of magnesium deficiency needs clarification although deficient intake during prolonged periods of parenteral feeding or in the course of prolonged alcoholic episodes are important factors Aldosterone may have an influence as hypomagnesemia and negative magnesium balance has been found in primary aldosteronism (71b)

SULFUR

Sulfur is a constituent of all body cells being present in the sulfur containing amino acids of proteins Small amounts of inorganic sulfur are also present in tissues Sulfur is found in certain carbohydrates e g, chondroitin sulfuric acid in cartilage tendons and bone matrix It is a constituent of the sulfatides glutathione insulin biotin and thiamine (63) Little is known about the human requirement of sulfur but it is presumably closely related to the need of sulfur containing amino acids These are discussed in connection with protein metabolism (p 35)

IRON

Iron deficiency may be nutritional in origin or result from loss of blood, particularly from chronic hemorrhage Dietary deficiency of iron may be observed during the growth period, especially in infancy and adolescence, and during the reproductive life of the female The newborn infant has a certain amount of stored iron the quantity being related to maternal supply during pregnancy

Iron has a number of important functions in the body It is an essential component of the hemin chromoproteins, hemoglobin, myoglobin, the cytochromes, peroxidase and catalase All of these play vital roles in the transport and utilization of oxygen for energy requirements (72)

Knowledge of certain features of iron metabolism is necessary for estimation of the adequacy of dietary intake and for diagnosis of potential iron deficiency before overt anemia occurs Many factors influence iron absorption and once iron is absorbed, only small quantities are lost from the body (72) Studies with radioactive iron indicate that absorption of iron salts is dependent on bodily need normal adults absorb only small amounts whereas persons with iron deficiency anemia absorb much larger quantities Moore and Dubach (73) have shown that normal subjects absorb about 10 per cent of iron from foodstuffs During the growth period, absorption appears to be related to requirement and ranges from 8 to 28 per cent An increase in absorption occurs in the latter months of pregnancy presumably due to fetal need

It has been postulated that absorption is regulated by an iron containing protein ferritin, in the intestinal mucosa According to this theory, iron becomes attached to the iron free form of this protein apoferretin in the mucosal cell to produce ferretin and is subsequently re-

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leased from ferretin at the blood stream end of the cell Apoferretin is presumably formed in the mucosal cell in response to a decrease in the iron stores of the body

Factors other than bodily need which may influence absorption of dietary iron include 1) The chemical nature of the iron in the food, i e , compounds which can be readily converted into ionized form are more available, as is ferrous as compared to ferric iron, 2) the acidity of the gastric juice (of relatively minor importance) and 3) the quantity of phosphates and phytates in the diet which can combine with iron to form insoluble salts Ascorbic acid enhances iron absorption, while administration of hydrochloric acid and antacids are without significant effect These factors must be considered in evaluating the physiologically available iron of the diet

Iron is transported in the serum in ferric form attached to a specific beta-1 globulin, siderophilin, also called transferrin The normal level of serum iron ranges from about 80 to 180 μg/100 ml while the maximum iron binding capacity of serum varies from 300 to 360 μg/100 ml Thus the beta 1-globulin is normally about 33 per cent saturated with iron Measurement of these levels are important in the diagnosis of iron deficiency as will be discussed subsequently

The total amount of iron in the body is about 4 to 5 gm of which approximately 72 per cent is found in hemo globin, slightly over 3 per cent in myoglobin, 0 2 per cent in parenchymal iron including that present in cytochromes, catalase and peroxidase and the remaining 23 per cent or more as storage iron (72) Iron is stored in two forms, ferritin and hemosiderin in the liver, spleen and bone marrow The extent of the iron stores of the body may be measured by estimating the amount of hemosiderin in bone marrow

Iron excretion is extremely small, only about 0.5 to 1.5 mg daily by all routes including urine, bile, sweat, intestines, loss of hair and desquamation of body cells. In view of the conservation of iron by the body and its continuous reutilization, the dietary requirement is much less than the amount of iron needed daily in the formation of hemoglobin (26-27 mg.). In the normal adult, requirement represents only replacement of the iron lost through excretion. Moore and Dubach (73) have suggested that the adult male must assimilate 0.5 to 1 mg. of iron daily to maintain balance, the adult female 1 to 2 mg. daily. Normal women lose an average of 1 mg. per day in the menses which accounts for the higher requirement. During pregnancy, an average of 2.7 mg. of iron per day is supplied to the fetus, thus increasing maternal need by this amount. During growth, there is an additional requirement for the building of new tissues and expansion of blood volume. The increment for growth amounts to 0.3 to 0.6 mg. daily in the first 20 years of life. Since only about 10 per cent of food iron is absorbed, the daily dietary requirement for iron is determined by multiplying physiologic need by a factor of 10. Recommended dietary allowances are of this order (Table 3). In pathologic conditions which are associated with blood loss, requirement is greatly increased. Gastrointestinal disturbances such as diarrhea, achlorhydria or intestinal disease may interfere with absorption and enhance dietary need. Consideraable iron may be lost by regular blood donors.

Iron Deficiency

Cartwright and associates (17) have pointed out that iron deficiency may occur in two forms: latent and manifest. The clinician commonly thinks of microcytic hypo-

chromic anemia as the outstanding feature of iron deficiency but before anemia occurs, deficiency is relatively far advanced Diagnosis of latent iron deficiency is dependent upon laboratory procedures which demonstrate a depletion of bodily iron stores, a reduced level of plasma iron, or an increased total iron binding capacity of the plasma Presumably the first change in deficiency is diminution of available iron stores which may be estimated by the simple method of Rath and Finch (17) The amount of hemosiderin in unstained bone marrow smears is graded 0 to 6 plus, in iron deficiency no hemosiderin or only a trace will be noted

The plasma iron level is decreased in all patients with manifest iron deficiency and in most patients with depleted tissue stores In iron-deficiency anemia a concentration of less than 50 μg per 100 ml is usually observed Unfortunately, hypoferremia is not specific for iron deficiency and is encountered in association with infections, even with such mild ones as the common cold Nevertheless, estimation of plasma iron is of value in assessing the adequacy of nutrition for if normal levels are obtained manifest deficiency is ruled out and iron stores have not been exhausted

Determination of the iron binding capacity of plasma will differentiate between hypoferremia due to iron deficiency and that associated with infection In the former total iron binding capacity is increased to over 400 μg/100 ml, in the latter it is decreased In iron deficiency anemia, in view of the hypoferremia and increased iron binding capacity, the saturation of the protein which carries iron is reduced from about 33 to less than 10 per cent

The anemia of manifest iron deficiency is characterized by small cells which are poorly filled with hemoglobin The severity of the anemia is usually proportion-

ate to the extent of iron deficiency Deficiency can be suspected by examination of a properly prepared and stained blood smear The presence of microcytes with pronounced central pallor are almost specific, only Thalassemia, a rare condition, need be ruled out This can be done readily by looking for target cells, stippling and nucleated red cells, as well as by physical findings, normal plasma iron, reduced iron binding capacity and increased hemosiderin in the bone marrow

The anemia of iron deficiency can be characterized more adequately by estimation of mean corpuscular volume (M C V) and mean corpuscular hemoglobin concentration (M C H C) both of which are reduced below the normal values of 82-92 cubic microns and 32-34 per cent respectively In order to obtain reliable figures for M C V and M C H C , the volume of packed red cells, hemoglobin concentration, and erythrocyte counts must be determined with great accuracy With proper techniques, accuracy of the determination of volume of packed red cells may be about ±1 per cent, that of hemoglobin concentration about ±2 per cent and of erythrocyte counts ±11 per cent In nutrition surveys, determination of hemoglobin in conjunction with stained blood smears can suffice as indicators of iron deficiency anemia, although estimation of the volume of packed erythrocytes gives additional useful information

In iron deficiency anemia the clinical findings are those common to all anemias of comparable severity Pallor of the skin and mucous membranes fatigability, weakness giddiness and syncopal attacks are observed frequently Heart failure of the high output type may develop In children there is retardation of growth In some subjects glossitis characterized by papillary atrophy angular stomatitis and dysphagia may be noted In anemia of consider-

able chronicity, the finger nails become flattened and concave giving them a spoon shape to which the term koilonychia has been applied

Iron Excess

Iron in excessive amounts may be toxic Large amounts of iron are stored after frequent transfusions or intravenous injections of iron In hemochromatosis, which probably represents an inborn metabolic abnormality, iron is absorbed in excessive amounts and massive deposits accumulate in the tissues especially in the liver, pancreas, adrenals and other endocrine glands In this disease, cirrhosis of the liver, pancreatic fibrosis and adrenal insufficiency are observed Acute toxicity may result from accidental ingestion of medicinal iron and fatalities have been reported (75) Characteristic symptoms are severe vomiting often of blood, watery stools which later become tarry, and profound shock The pulse is rapid weak or imperceptible and the blood pressure is low Hypotonia hyporeflexia, dilated pupils, and a semicomatose or comatose state complete the clinical picture Death has occurred in from 4 to 40 hours

COPPER

The role of copper in human nutrition remains obscure and the requirement is unknown Studies in animals indicate that copper is necessary for the synthesis of the iron porphyrin ring In copper deficiency, the tissue content of cytochrome oxidase has been found to be markedly decreased (76) It has been shown that 2 0 mg of copper daily will maintain balance in an adult The diet usually furnishes 2 0 to 5 0 mg and since copper is so widely distributed in foods, it seems likely that an adult would succumb to caloric inadequacy before severe depletion of

copper could develop (17) The plasma concentration of copper is usually greater than 90 µg/100 ml Although hypocupremia has been found in the newborn and in hepato lenticular degeneration, tissue stores of copper are increased in both conditions Hypocupremia and an increased excretion of copper have been found in the nephrotic syndrome but when an anemia was present, there was no hematopoietic response to copper (17) To date, no definite evidence of copper deficiency in man has been presented Copper has not been shown to be of assistance in the treatment of hypochromic microcytic anemia in adults and only rarely is copper a limiting factor in blood formation in infants

COBALT

A deficiency of cobalt, per se, has never been recognized in the human subject Positive balance may be maintained with an intake of 5 µg daily Cobalt is essential for the activity of certain enzymes and is an integral part of the vitamin B_{12} molecule Evaluation of vitamin B_{12} nutrition is discussed in another section (p 126)

IODINE

The physiologic importance of iodine rests in its essentiality for the formation of the thyroid hormone which maintains control of energy metabolism through some unknown pathway The human requirement for iodine is about 1 µg per kilogram of body weight daily for basal needs and an additional 2 µg/kg for the maintenance of total metabolic activity The suggested daily allowance for an adult is 0 15 to 0 30 mg daily (0 002 to 0 004 mg/kg body weight) (4a) This amount can be supplied by the regular use of iodized salt

Iodine is absorbed from the small intestine at an exponential rate which varies with the level of thyroid ac-

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thyroid hormone This indicates that iodine is essential for growth, it is also essential for normal fertility and for lactation

Diagnosis of endemic goiter is suggested by the presence of an enlarged thyroid gland in a person living in an area where iodine intake is low Other causes of hypertrophy of the thyroid must be ruled out Thyroid enlargement is most commonly seen during puberty and in pregnancy when the need for iodine is increased In goitrogenous areas, the urinary excretion of iodine is low, ranging from less than 10 to about 65 μg daily, as compared to 72 to 343 μg daily in nongoitrogenous areas The protein bound iodine level in blood is usually within the normal range in persons with endemic goiter The uptake of I^{131} by the thyroid gland of these individuals is higher than that of euthyroid persons in other areas of the world Hence, this test is not useful in the diagnosis of hyperthyroidism in regions where endemic goiter is prevalent (78)

tivity (77) Iodine is taken up by the thyroid gland which converts it to di iodotyrosine and thyroxine In normal persons, the iodine uptake is proportional to blood con centration Measurement of the uptake of radioactive iodine is a useful procedure in the diagnosis of thyroid disease, uptake is increased in hyperthyroidism and de creased in hypothyroidism altho numerous factors can in fluence findings

The iodine in blood is in two forms, inorganic and protein-bound iodine, the later presumably representing the circulating thyroid hormone The total iodine of whole blood ranges from 3 to 30 μg/100 ml, usually 8 12 μg, while protein bound iodine varies from 3 to 8 μg, mean 5 6 μg The level of protein bound iodine is decreased in hypothyroidism and increased in hyperthyroidism and during pregnancy Urinary excretion of iodine is depen dent upon dietary intake the activity of the thyroid gland and probably other factors

Iodine Deficiency

Iodine deficiency leads to the development of endemic goiter In areas of the world where the iodine content of the water, soil and foods grown therein are low, the incidence of endemic goiter is high Goiter can be pro duced by factors other than iodine deficiency Goitrogenic agents have been found in foods, especially in those of the cabbage family and a number of synthetic chemical com pounds have goitrogenic activity In endemic goiter, the thyroid gland may contain less than 1 mg of iodine whereas the normal thyroid contains 8 to 10 mg

In areas where endemic goiter is prevalent, congenital hypothyroidism or cretinism is observed In cretinism growth may be stimulated and normal mental and physical development attained by continuous administration of

mins in a single prescription except in situations of gross dietary inadequacy or in pathologic states requiring prolonged parental feeding On the other hand, it is often essential to furnish, at the same time, each of the vitamins which function in various stages of a given metabolic process In view of the above, diagnosis of vitamin malnutrition must be considered from the standpoint of individual chemical compounds and not the group as a whole This is true in spite of the fact that certain of the vitamins, the "B group in particular, are found closely associated in nature and that multiple deficiency is more often encountered than deficiency of a single factor Appreciation of the complexity of deficiency and of the interrelationships among nutrients is necessary if correct diagnosis is to be achieved

Vitamins, or their derivatives, have been shown to function in metabolism in combination with proteins in the promotion of catalysis of certain body processes Most commonly, vitamin derivatives are coenzymes while proteins form the corresponding apo enzymes It seems logical to assume that altered biochemical reactions precede clinical signs of vitamin deficiency If this is the case tests of specific metabolic function should permit diagnosis before overt physical abnormalities make their appearance As yet few tests of metabolic function are available Appropriate experimental materials such as specimens of tissue, are not easily obtained In the limited studies which have been conducted, metabolic alterations have been found to be quantitative rather than qualitative and suitable norms and variability among individuals around these norms have not been established In addition as Snell has indicated, most of the enzymes examined thus far "have not shown readily measurably changes before other more readily observable deficiency symptoms

VITAMIN NUTRITION

GENERAL OBSERVATIONS

IN MANY ways it is unfortunate that a number of the chemical substances which are dietary essentials have been grouped together in a single category designated vitamins If the entire group of 15 or more vitamins is considered together, the only characteristic that all members have in common is essentiality in small amounts in the diet due to the body s inability to manufacture them from simpler compounds Even this statement is not entirely true Many animals can synthesize ascorbic acid, and all animal species tested, including man, manufacture niacin from the amino acid tryptophan In some instances, synthesis of a vitamin by bacteria in the intestinal tract may furnish a sufficient amount of a particular vitamin e g , vitamin K, to largely eliminate the necessity of its inclusion in the diet

Modern nutritional science has advanced to such an extent that each of the vitamins should be considered separately in terms of its chemical structure, requirement and function in the body While there are close functional interrelationships between many of the vitamins, others are not so related In addition there are as close or closer interrelationships between vitamins and minerals, and between vitamins and amino acids as there are among the vitamins themselves Pathologic conditions which influence the requirement or utilization of one vitamin may not affect that of another There is little scientific justification for the therapeutic use of all of the vita-

cream), and as the pro-vitamin, carotene, which is present in green and yellow vegetables and in fruits Carotene is converted to vitamin A ester presumably in the intestinal wall The availability of carotene in food varies widely, *a factor which must be considered in estimating* the potential vitamin A value of the diet Since vitamin A is fat soluble, absorption is facilitated by the simultaneous absorption of fat and deficiency may be encountered when absorption of fat is decreased The latter occurs when bile is absent from the intestinal tract, in infectious hepatitis, and in steatorrheas, i e, sprue, celiac disease, pancreatic fibrosis and idiopathic steatorrhea. Administration of liquid petroleum with meals interferes with absorption of carotene and, to a lesser extent, of vitamin A Vitamin A deficiency may be encountered in diabetes mellitus and hypothyroidism in which diseases conversion of carotene to vitamin A seems to be impaired Since the liver is the chief site of storage of vitamin A, deficiency may be associated with chronic liver disease, particularly advanced cirrhosis

The minimum daily requirement of vitamin A is 20 I U or 6 μg per kilogram of body weight, if supplied by the preformed vitamin and three to five times as much if furnished by dietary carotene Quantities above minimum are needed to provide for significant storage and in animals, for normal reproduction The recommended allowance of the Food and Nutrition Board for vitamin A is 5000 I U daily for an adult receiving a mixed diet which supplies two-thirds of the vitamin as carotene (See Table 3) In using the dietary record for evaluating vitamin A nutrition it should be remembered that large amounts of the vitamin may have been stored in the liver and that many months may be required for depletion of these reserves (79)

appear (17) This last statement may be explained best by presuming that the proper enzymes have not been chosen for study It would not be anticipated that all enzymes dependent on a given vitamin would decrease in activity at the same rate as deficiency progresses Enzymes requiring the highest concentration of coenzyme for activation would be most rapidly affected and hypo function of these enzymes presumably should lead to the earliest clinical signs of deficiency (17) When enzymes unusually sensitive to vitamin deficiency are discovered, it may be possible to devise suitable "load" tests which will cause the enzymes to work at maximum capacity Resulting metabolites can be measured and findings in experimental and control subjects compared Such tests would obviate the necessity for analysis of tissue samples A few procedures of this type have been proposed relative to vitamin B_6 (p 119) and thiamine (p 107) It might be anticipated that no single test of specific metabolic function will suffice in detecting deficiency or adequacy of a given vitamin under all conditions

Minimal daily requirements of some of the vitamins essential to man have been determined, little is known of optimal needs Undoubtedly, numerous factors influence requirement For vitamin requiring bacteria, the optimal intake of a vitamin cannot be determined apart from the total makeup of the ration (17) It seems likely that this may apply to vitamin needs of animals and man Varia*tion in requirement may be expected with changing* physiologic conditions and in pathologic states

VITAMIN A

Vitamin A an unsaturated alcohol, is supplied in the diet as the preformed vitamin which is found only in animal tissues (especially liver, egg yolk, butter and

Xerosis of the skin with hyperkeratinization, also called toad skin or phrynoderma, is probably another manifestation of vitamin A deficiency The relationship of localized areas of keratosis of the hair follicles or of permanent "goose flesh" to vitamin A deficiency is less well documented Follicular hyperkeratosis is observed in conditions unassociated with vitamin A deficiency and has not been produced in experimental deficiency in man

In animals, cornification of the vaginal smear is noted in vitamin A deficiency and epithelial changes in the urinary tract have been associated with formation of calculi In human subjects, administration of vitamin A has been reported to induce improvement in senile vaginitis but a role for vitamin A deficiency in formation of renal calculi remains to be demonstrated In infants deficient in vitamin A, keratinization of the respiratory epithelium has resulted in blockage of small bronchioles, bronchiectasis and atelectasis At one time these findings were attributed erroneously to infection which led to the mistaken idea that vitamin A was an anti infective vitamin

Estimation of the level of carotene and vitamin A in blood serum are of assistance in the diagnosis of deficiency The concentration of carotene reflects recent dietary intake in most instances and ranges from about 75 to 200 µg per 100 ml in well nourished subjects Hypercarotenemia is associated with consumption of large amounts of carotene or with diseases in which conversion of vitamin A to carotene is impaired, such as diabetes mellitus and hypothyroidism The concentration of vitamin A in the plasma ranges from 30 to 50 µg per 100 ml in well nourished children and adults (17) In vitamin A deficiency the concentration is usually below 15-20 µg per 100 ml and, at times, no vitamin A may be detected

The two important metabolic functions of vitamin A in man are the maintenance of normal epithelium and the formation of the retinal pigment, rhodopsin, of which vitamin A is an integral part (80) Rhodopsin is necessary for vision in dim light When the dark adapted retina is exposed to light, rhodopsin is changed to retinine, which is vitamin A aldehyde, plus a protein Vitamin A is needed for regeneration of rhodopsin since a certain amount is lost in the process of breakdown

In certain animal species, vitamin A has been shown to influence bone growth Also in animals, deficiency of this factor during pregnancy has resulted in congenital malformations in the offspring

Vitamin A Deficiency

The principal signs of vitamin A deficiency in human subjects are night blindness and xerophthalmia (80) Mild degrees of vitamin A deficiency may be determined by measuring the rate of recovery of dark adaptation following exposure to bright light This procedure requires special instrumentation and rigid techniques as there are many sources of error Its usefulness is limited largely to research studies

Xerophthalmia which is encountered rarely in the United States, is manifested by decreased lacrimal secretion, keratinization of the corneal and conjunctival epithelium and Bitot s spots which are triangular conjunctival thickenings due to accumulations of white, foam like epithelial cells lateral to the cornea Bitot s spots must be differentiated from pingueculae and pterygia which are unrelated to vitamin A deficiency When vitamin A deficiency reaches an advanced stage infection of the eye may occur with destruction of the cornea panophthalmitis, and blindness

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Unfortunately from a diagnostic standpoint, a decrease in concentration of vitamin A *in serum occurs in conditions* unassociated with depletion of vitamin A stores of the body. Such decreases are observed in a number of febrile illnesses, the level returning to normal following recovery without administration of vitamin A. In the absence of such illness, a low plasma level of vitamin A *is presumptive evidence of depletion of reserve stores in* the liver.

The absorption of vitamin A may be tested by means of a tolerance test in which blood levels are determined at intervals after oral administration of large doses of the vitamin (p. 59). Comparison of absorption following administration of oily and aqueous preparations of vitamin A may also prove useful.

Vitamin A is not found in the urine of normal subjects but may be excreted in certain pathologic states, e.g., pneumonia, obstructive jaundice or chronic nephritis. In the nephrotic syndrome, high concentration of serum vitamin A has been noted following administration of the vitamin due perhaps to impaired metabolism (81).

Hypervitaminosis A

Since vitamin A which has been absorbed is not excreted under normal conditions it follows that repeated ingestion of large amounts may lead to excessive accumulation and toxicity. A number of instances of hypervitaminosis A have been reported most of them in children (82). Abnormal findings have included anorexia loss of weight, irritability, low grade fever, pruriginous rash sparseness of hair changes in bone (hyperostoses and periosteal elevations) hepatomegaly, splenomegaly and hypoplastic anemia. The concentration of vitamin A in serum is high usually above 100 µg per 100 ml. It has

been postulated that the syndrome may be due to hepatic dysfunction The minimal toxic dose reported is about 75,000 I U daily for a period of six months (82)

VITAMIN B COMPLEX

The vitamin B complex comprises a number of factors differing widely in chemical structure, most of which have been found to be essential in human nutrition Many of these vitamins are components of one or more coenzymes which function importantly in intermediate metabolism Such roles have been demonstrated for thiamine, riboflavin, niacin, pyridoxine and pantothenic acid It seems likely that the "anti anemic" vitamins, folic acid and vitamin B_{12} will be found to act in a similar manner Choline, often considered a member of the B complex, is undoubtedly important in human nutrition but is not an essential dietary constituent as it may be formed in the body from other compounds Presumably man requires biotin, but little is known about the function of this vitamin Inositol has not been shown to be essential in human nutrition

Deficiency of vitamins of the B complex is one of the forms of malnutrition encountered frequently in medical practice Since many of the B vitamins have a common distribution in foods, multiple deficiency is observed more often than deficiency of a single compound Since some of these vitamins are closely interrelated in metabolic processes, the clinical signs of deficiency may be similar when the dietary supply of any one of several factors is inadequate Hypervitaminosis is not a problem with members of the B group of vitamins because amounts in excess of requirement are excreted in the urine

Numerous pathologic states may be precipitating or contributary causes of vitamin B complex deficiency Dis-

eases in which the metabolic rate is above normal, such as hyperthyroidism, febrile states or leukemia, increase the requirement of thiamine and probably also of riboflavin and niacin although definitive data are not available for the last two vitamins Since these vitamins function in the metabolism of carbohydrate requirement is increased when diets are high in starch and sugar or when intravenous glucose is used as the sole source of alimentation It seems likely that need may be increased following severe trauma

The B vitamins may be poorly absorbed or lost from the body in diarrheal diseases, inflammatory lesions of the intestinal tract and in congestive heart failure or other conditions associated with edema of the intestinal mucosa There is evidence that vitamin B complex deficiency per se may cause poor absorption from the intestinal tract Malabsorption is demonstrated by flat glucose and fat tolerance tests and abnormalities in the roentgenographic appearance of the small intestine The changes observed following barium administration consist of loss of the normal 'herringbone pattern, hypersegmentation and disturbances in motility

In diabetes mellitus and cirrhosis of the liver, signs of vitamin B complex deficiency are observed frequently In both conditions vitamin utilization may be defective and in the latter disease anorexia and an inadequate intake of these factors are the usual findings

At times, administration of certain antibiotics may lead to vitamin deficiency although under other circumstances antibiotics may spare vitamin requirement (83) The possibility that prolonged antibiotic therapy may induce deficiency must be kept in mind Lesions suggestive of deficiency must be differentiated from similar change due to complicating *fungus infections which are not uncommon*

THIAMINE

Thiamine, or vitamin B_1 is a water soluble compound containing the thiazole and pyrimidine rings It is readily destroyed by heat and considerable loss may occur in the preparation of food Although thiamine is widely distributed in nature, rich sources are few, namely, peas, beans, lean pork, peanuts, oatmeal, whole wheat and enriched flour and bread However, milk, vegetables and fruit contribute appreciable quantities to the diet

Thiamine requirement is related to caloric intake, the minimal need being approximately 0 25 to 0 30 mg per 1000 calories The recommended allowance of this vitamin is 0 5 mg per 1000 calories (Table 3) This large factor of safety seems desirable since bodily stores of thiamine are not large and may be exhausted rapidly in diseases associated with elevated metabolism and, perhaps, in other stress situations

Thiamine functions in the body as a coenzyme, cocarboxylase, which is thiamine pyrophosphate and possibly also as a coenzyme in combination with lipoic acid, lipothiamide Thiamine coenzymes are important in the decarboxylation of α keto acids such as pyruvic acid Substances formed include acetic acid, acetyl phosphate and acetyl coenzyme A, the last being of great importance as it feeds into the tricarboxylic acid cycle to provide energy In thiamine deficiency, pyruvate accumulates in the blood and tissues and there is a change in the lactate pyruvate ratio These findings are useful in the diagnosis of deficiency

Thiamine Deficiency

The outstanding clinical findings in advanced thiamine deficiency are peripheral neuritis (dry beriberi) and heart disease with edema (wet beriberi) The diagnosis

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jects with cirrhosis of the liver, peripheral neuritis improves following thiamine administration

In beriberi heart disease, palpitation, precordial pain and dyspnea on exertion may be noted and cyanosis is common Bradycardia at rest with tachycardia on exertion is seen early, subsequently, tachycardia may be persistent The pulse pressure is wide, with a decrease in the diastolic pressure and occasionally a slight increase in systolic pressure There is enlargement of both the right and left sides of the heart, the former predominating Systolic murmurs and, rarely, diastolic murmurs may be heard over any of the valve areas Gallop rhythm and embryocardia are common Precordial and epigastric pulsations are observed frequently, the neck veins are dilated and may pulsate The liver is enlarged and pulsations may be observed here as well Edema is often massive and there may be transudation into serious cavities Oliguria is a characteristic finding

Roentgenographic examination of the heart shows an increase in the transverse diameter and, at times, enlargement of the pulmonary conus Electrocardiographic abnormalities include lowering of QRS complexes, flattening of the T-waves, prolongation of the Q T interval and deviations of the S-T segment Occasionally, premature contractions, axis deviation or abnormalities of the P waves may be noted The cardiac failure is of the high output type, circulation time being normal or decreased Venous pressure is elevated In severe cardiac beriberi, acute peripheral circulatory collapse and sudden death may occur

The diagnosis of thiamine deficiency heart disease is dependent on dietary history elimination of other etiologic factors, the presence of a high output type of cardiac failure, coexistent peripheral neuritis and response to

of thiamine deficiency is not easy, however, particularly in early stages since many findings are nonspecific and common to other pathologic states In experimentally in duced deficiency, early findings include anorexia fatiga bility, apathy, epigastric pain, nausea and vomiting and psychic and emotional disturbances such as irritability, *moodiness, vague fears and depression (84) Daum and* associates (84b) reported that the most sensitive physio logic *indices of an inadequate supply of thiamine* were decreases in maximum work output and in mechanical efficiency

Early signs of polyneuritis are burning of the soles of the feet and numbness and tingling of the feet and legs The first indication of heart disease may be ab normalities in the electrocardiogram As polyneuritis becomes more severe, hyperesthesia and, later, an algesia develops beginning distally in the toes and progressing upward Shooting pains in the legs *muscle* cramps, tenderness of the calves, weakness, a decrease or absence of *the Achilles and patellar* reflexes and muscle atrophy may be observed A test for neuritis which is widely used in the Orient is inability to rise from the squatting position Complete flaccid paraly sis with foot drop occurs in advanced deficiency Changes in the upper extremity are rarely observed until involvement of the lower extremity has become *severe* Edema *may be present even in the absence* of heart failure, the explanation for which is unknown

The peripheral neuritis of chronic alcoholism is often due to thiamine deficiency It is explicable by the poor dietary intake of thiamine and not by the ingestion of alcohol which actually requires less thiamine for utiliza tion than does glucose Neuritis in subjects with diabetes is only rarely due to thiamine deficiency In some sub-

jects with cirrhosis of the liver, peripheral neuritis improves following thiamine administration

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The diagnosis of thiamine deficiency heart disease is dependent on dietary history elimination of other etiologic factors the presence of a high output type of cardiac failure coexistent peripheral neuritis and response to

therapy with thiamine Digitalis is of little value in the treatment of beriberi heart disease On the other hand, administration of thiamine is followed by diuresis and gradual reversal of pathologic changes, the heart size and electrocardiographic findings *returning to normal*

Infantile beriberi occurs in breast fed infants of mothers who have thiamine deficiency It has been observed rarely in the United States and has been studied largely in Japan and other Far Eastern countries (85) The earliest and most important symptoms are anorexia and vomiting Urine becomes scant the pulse and respiration labile and rapid Cranial nerve involvement is common particularly hoarseness due to vocal cord paralysis and ptosis *of the eyelid The child may whine in a plaintive manner* and the 'beriberi cry is said to be characteristic Diagnosis is made when acute symptoms supervene such as paroxysms of pain associated with rigidity of the body but not true convulsions Cyanosis, engorgement of the neck veins and a small rapid pulse are frequent findings Death often occurs within twelve to twenty four hours A less common chronic form of the disease has been described which is characterized by obstinate constipation, vomiting unrelated to meals, restlessness at night, enlargement of the heart, pallor and weakness

Several laboratory tests have been developed which are useful in the diagnosis of thiamine deficiency (17) The urinary excretion of thiamine is linearly related to the intake except at low levels although there is marked individual variation Measurement of thiamine excretion in 24 hours is useful in reflecting dietary supply In order to evaluate the extent of depletion of tissue stores a test dose of thiamine may be given orally or intramuscularly and the excretion in the urine measured for a period of time thereafter Well nourished subjects who are given

1 0 mg of thiamine intramuscularly excrete 100 200 μg in the subsequent four hours An excretion of less than 50 μg with this test is usually considered evidence of deficiency

In nutrition surveys, determination of excretion of thiamine in random specimens of urine in relation to excretion of creatinine may be used for an approximate estimate of the adequacy of thiamine nutrition

Estimation of the concentration of thiamine in blood does not appear to be of much value in appraising nutritional status of individuals although it may reflect, to an extent, the intake of population groups (86) The concentration of pyruvic acid in blood rises as thiamine deficiency becomes evident but cannot be used as a nutritional index since other factors, such as activity and ingestion of glucose, influence blood levels of pyruvic acid The ratio of lactic acid to pyruvic acid in blood was found by Stotz and Bessey (87) to be useful in determining thiamine adequacy Horwitt (88) has proposed determination of a "carbohydrate index" for detecting early thiamine deficiency In this test glucose, lactic acid and pyruvic acid are measured in blood one hour after giving 1 8 gm of glucose per kilogram body weight and 5 minutes after a standard exercise test The index is determined from the formula

$$C\,I = \frac{\left(L - \frac{G}{10}\right) + \left(15P - \frac{G}{10}\right)}{2}$$ where C I is

cardiac index, L lactic acid P pyruvic acid and G glucose An index of more than 15 suggests thiamine deficiency

Thiamine deficiency appears to be related to several syndromes other than peripheral neuritis and heart disease A type of optic or retrobulbar neuritis associated with paralysis of extra ocular muscles, occurred in con-

centration camps in World War II and appeared to be due, at least in part, to thiamine deficiency Wernicke s encephalopathy, characterized by ophthalmoplegia, nystagmus, ataxia and mental disturbances is a syndrome due to deficiency of thiamine (89) Thiamine, and other vitamins of the B complex, have proved valuable in the treatment of delirium tremens and other acute alcoholic psychoses The susceptibility of the nervous system to thiamine deficiency may be explained by its dependence on glucose metabolism

Intolerance to large doses of thiamine has been reported and is presumably due to simple chemical toxicity, principally through the formation of excessive amounts of acetylcholine and histamine (90)

RIBOFLAVIN

Riboflavin is a water soluble, yellow pigment with green flourescence which is widely distributed in foods of both plant and animal origin While relatively stable to heat it is destroyed on exposure to light, hence considerable loss can occur in some foods such as milk The minimal daily requirement appears to be about 0 6 0 7 mg in the adult, 0 4 0 5 mg in the infant The recommended intake is considerably higher than this 1 4 to 1 6 mg for the adult (Table 3), in order to supply adequate tissue reserves Flavoproteins function in a number of important enzyme systems in tissue respiration

There is a close relationship between the retention of riboflavin and the retention of protein It seems likely, therefore that abnormalities of riboflavin metabolism may be associated with severe injuries burns hemorrhage and infection Riboflavin deficiency often occurs in association with lack of niacin and signs of an inadequate supply of riboflavin have been confused with those of pellagra

Manifestations of riboflavin deficiency have been observed in prolonged febrile illnesses, such as rheumatic fever, tuberculosis and sub-acute bacterial endocarditis, in malignancy, hyperthyroidism, cardiac failure, diabetes mellitus and diseases of the gastrointestinal tract. Deficiency occurs with greater frequency in older than in younger age groups.

Riboflavin Deficiency

Symptoms of riboflavin deficiency are photophobia, burning of the eyes, lacrimation, soreness of the lips and tongue and cracks at the corners of the mouth. Characteristic physical findings are cheilosis, angular stomatitis, glossitis, a seborrheic type of dermatitis and superficial vascularization of the cornea (91). The lips may be swollen, red at the line of closure and denuded, maceration, crusts and fissures are present at the angles of the mouth. Common sites of seborrheic dermatitis are the nasolabial and nasomalar folds, the outer canthi of the eyes and the ears. Scrotal dermatitis was a frequent finding in experimentally induced riboflavin deficiency (92). The tongue may be magenta in color with papillary atrophy or hypertrophy, and fissures may be present. None of these lesions is pathognomonic of riboflavin deficiency although all of them have been induced in human subjects receiving diets inadequate in riboflavin. Cheilosis and angular stomatitis have been observed in experimental niacin deficiency and following the administration of desoxypyridoxine (93). Lesions of the lips may be the result of exposure to weather while angular fissures occur in association with malocclusion and poorly fitting dentures. Vascularization of the cornea may be due to trauma or infection and seborrheic dermatitis may be related to lack of vitamin B_6 or be unassociated with malnutrition

Glossitis is common in deficiency of many of the B complex vitamins

In animals, the ability of the liver to inactivate estradiol is reduced in riboflavin deficiency It has been suggested that a similar change may occur in man In animals, also, riboflavin deficiency during pregnancy has resulted in abortion and in abnormalities of the embryo The relationship of riboflavin deficiency to congenital defects in man remains unknown

Diagnosis of riboflavin deficiency is dependent on a history of low dietary intake, the presence of several of the lesions mentioned above and, at times, association with some disease which influences riboflavin metabolism Laboratory studies may be of assistance in diagnosis The concentrations of free riboflavin and flavin mononucleotide in plasma have been found to decrease in many, but not in all, subjects when the intake of riboflavin is restricted, while plasma flavin dinucleotide and total white blood cell riboflavin show little change (94) The concentration of riboflavin in red blood cells decreases significantly during periods of restricted intake Bessey (94) has suggested that red blood cell contrations below 14 μg/100 ml can be interpreted as meaning a level of intake that if continued, will lead to clinical manifestations of deficiency Concentrations above 20 μg/100 ml indicate an adequate ribofllavin intake While analysis of riboflavin in plasma is useful in determining nutritional status, it may be that determination of riboflavin in erythrocytes will prove to be a better measure of tissue stores The latter test requires further study

Measurement of the urinary excretion of riboflavin is of limited value in assessment of nutritional status (17) An excretion of more than 200 μg of riboflavin in 24 hours is seldom associated with significant tissue depletion, and

an excretion of more than 150 μg per gram of creatinine in a random specimen of urine is usually indicative of tissue saturation (17) However, excretions of this order of magnitude do not necessarily indicate normalcy The output of riboflavin is increased in acute but not in chronic starvation, in diabetes mellitus, in conditions in which nitrogen balance is negative and after the administration *of certain antibiotics Physical activity also in*fluences excretion

In subjects receiving constant diets, excretion following small test doses (less than 2 mg) has been found to reflect dietary intake Estimation of excretion for four hours following parenteral administration of 1 0 mg of riboflavin is a procedure which seems to merit further study in the evaluation of riboflavin nutrition

A controlled therapeutic test is valuable in corroborating the diagnosis of riboflavin deficiency, lesions due to an inadequate supply of riboflavin heal rapidly when the vitamin is administered

NIACIN

Niacin deficiency in its classical form, pellagra, is encountered chiefly in population groups in which corn furnishes the staple cereal of the diet The association of pellagra with diets high in corn has been explained to a large extent by recent research It has been shown that the amino acid tryptophan is converted by the body through a series of chemical reactions to the vitamin niacin (95) One of the proteins of corn zein, is known to be low in tryphtophan The low tryptophan and niacin content of corn diets accounts in large part for their pellagragenic effect The possibility that corn contains some inhibitory factor which influences niacin requirement has not been ruled out completely but if such a

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nucleotide, and coenzyme II, triphosphopyridine nucleotide These enzymes, which are found in all cells, are concerned in glycolysis and tissue respiration

Niacin Deficiency

Early signs of niacin deficiency are lassitude, anorexia, mild digestive disturbances, especially "heartburn," glossitis diarrhea, and psychic and emotional changes such as anxiety, irritability and depression The tongue is sore, red, often swollen and there is hypertrophy or atrophy of the papillae Cheilosis, angular stomatitis and seborrheic dermatitis of the nasolabial folds have been observed in experimental niacin deficiency, although the diet contained an adequate amount of riboflavin (37, 96) The occurrence of similar lesions in niacin and riboflavin deficiency attests the close metabolic relationship of these vitamins

In severe or prolonged deficiency, characteristic dermatitis extensive inflammation of mucous membranes and marked mental disturbances are observed The dermatitis involves the skin surfaces exposed to sun light or subjected to trauma or irritation In classical pellagra, the dermatitis in the early stages resembles sunburn, subsequently, bleb formation, secondary infection and pigmentation occur At times, the skin is so extensively in volved that bullae break and exfoliate leaving large denuded areas similar to those of a severe burn The lesions are bilateral symmetrical and clearly demarcated from the normal skin Areas most often involved are the backs of the hands and forearms, anterior surfaces of the feet and lower legs and the neck (Casal s necklace) The face may be involved and also the axilla groin, perineum genitalia, elbows knees and the area under the breasts In mild, chronic pellagra, only thickening hyperkeratin-

factor is present, it is of little practical importance (96) There is evidence that some of the niacin in corn is present in bound form which may be unavailable for absorption

Since tryptophan is a precursor of niacin, it is necessary to estimate the tryptophan as well as the niacin content of diets in determining the adequacy of niacin intake The ratio of conversion of tryptophan to niacin compounds is in the neighborhood of 60 to 1 that is, about 1 0 mg of niacin is formed from 60 mg of dietary tryptophan (97) Pellagra preventive foods include liver, lean meat peanuts potatoes, legumes milk and eggs, the last two foods furnish little niacin but are excellent sources of trpytophan Since niacin is stable to heat, loss in food preparation is minimal

The minimum niacin requirement of the adult is about 9 0 to 12 0 mg daily including that formed from tryptophan assuming a conversion ratio of 60 to 1 (4a) The requirement of the infant is about 5 mg daily Requirement appears to be related to body size and to caloric intake (96 97) Approximately 4 4 mg of niacin is needed for every 2000 calories furnished by the diet, but with low caloric intakes not less than 9 mg should be supplied In terms of body weight about 0 15 mg total niacin per kilogram will prevent pellagra

Infants have been maintained satisfactorily for several months on purified diets high in tryptophan and free of niacin *Whether the body's niacin requirement can be met solely by tryptophan remains unknown* Recommended allowances of niacin (Table 3) are about fifty per cent greater than minimum needs calculated on the basis of body weight or caloric intake

Niacin functions in the body as a component of two important coenzymes Coenzyme I, diphosphopyridine

nucleotide, and coenzyme II, triphosphopyridine nucleotide These enzymes, which are found in all cells, are concerned in glycolysis and tissue respiration

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Niacin functions in the body as a component of two important coenzymes Coenzyme I, diphosphopyridine

niacin deficiency appear shortly after this low level is reached

Estimation of urinary excretion of N^1Me and pyridone for 24 hours on a standard diet which furnishes about 10 0 mg of niacin and 1000 mg of tryptophan gives considerable information relative to niacin nutrition Patients with pellagra excrete less than 3 0 mg with this regimen and well nourished subjects 7 0 to 37 0 mg (99) This test would seem to merit further study The number of days required for maximum urinary excretion to be attained by subjects receiving the above standard diet, supplemented with 10 0 mg of niacinamide, has been suggested as a method of estimating the extent of depletion of tissue stores (100)

A number of test dose procedures have been suggested for evaluating niacin nutrition (17) One that has been used widely is estimation of urinary excretion of N^1Me during a period of four to five hours after administering 50 0 mg of niacinamide Such tests have not been satisfactory when applied to individuals but have given some information in nutrition surveys A smaller test dose 10 0 mg, and at least a 12-hour period of urine collection would be more informative Measurement of excretion of N^1Me and pyridone in random urine specimens in relation to creatinine output is being explored as a test for evaluating nutritional status of population groups

Measurement of total nicotinic acid or of coenzymes in blood has not proved useful in detecting niacin deficiency Normal concentrations have been found in patients with pellagra

Niacin deficiency occurs as a complication of a number of pathologic states in which food intake is restricted or in which there is interference with absorption or utilization of nutrients Subjects with chronic alcoholism cir-

ization, pigmentation and scaling of the skin may be evi dent, particularly over points of pressure

Severe inflammation of the entire gastrointestinal tract is found in advanced niacin deficiency glossitis, stoma titis, esophagitis with dysphagia, gastritis, diarrhea, usu ally watery but occasionally containing blood, and proc titis Involvement of other mucous membranes is evi denced by vaginitis and urethritis The psychiatric mani festations of severe pellagra include confusion, delusions, hallucinations, disorientation and stupor

Deficiency of riboflavin, thiamine and other B com plex vitamins may complicate the clinical picture of en demic pellagra Achlorhydria frequently accompanies niacin deficiency and an anemia, either macrocytic or hypochromic, may be observed The macrocytic anemia responds to folic acid rather than to niacin, while the hypochromic anemia usually represents deficiency of iron

A neurologic syndrome consisting of progressive stupor, grasping and sucking reflexes, and cogwheel rigidity of the extremities has been ascribed to acute niacin defici ency This syndrome has been noted in association with febrile illness and prolonged parenteral feeding with glu *cose and has been reported to respond to niacin* (98)

The diagnosis of mild niacin deficiency is not easy in the absence of characteristic dermatitis The presence of glossitis diarrhea and mild mental changes in a subject whose diet has been low in niacin and good protein is highly suggestive Laboratory findings may assist in cor- roborating the diagnosis Niacin is excreted in the urine largely as N^1 - Methylnicotinamide (N^1Me) and the 6- pyridone of N^1Me (pyridone) In subjects maintained on diets low in niacin and tryptophan, excretion of pyridone falls rapidly to less than 1 mg and excretion of N^1Me decreases gradually to 0 5 0 8 daily (37, 96) Signs of

observed in infants who received a proprietary liquid milk formula (103) Findings included irritability, easy startling, abdominal distention, muscular twitchings and convulsive seizures The electroencephalogram was abnormal in several instances Recovery followed a change of formula or administration of a large amount of pyridoxine Investigation indicated that the sterilization process had destroyed some of the vitamin B_6 in this milk preparation There had also been some change in the fatty acid composition of the mixture As a result of this unfortunate episode some knowledge of vitamin B_6 requirement was obtained Symptoms developed in infants who received 60 micrograms of vitamins B_6 per liter of milk while none occurred in infants fed 100 μg of vitaman B_6 per liter

Several attempts have been made to induce vitamin B_6 deficiency in adults (101) In one experiment, in which two subjects were maintained on a vitamin B_6 deficient diet for three weeks, excretion of xanthurenic acid after ingestion of tryptophan was increased (104) Xanthurenic acid is an abnormal product of tryptophan metabolism which appears in the urine in vitamin B_6 deficiency In another experiment one subject was maintained on a vitamin B_6 deficient diet for 54 days without developing any manifestations of deficiency disease Vilter and associates (105) studied the problem of vitamin B_6 deficiency by administering a pyridoxine antagonist desoxypyridoxine to adults some of whom also received a diet low in B complex vitamins Many of the patients became irritable depressed and sometimes somnolent Seborrheic dermatitis developed about the eyes in the nasolabial folds and in the eyebrows and spread to involve the face forehead chin up into the hair and down the neck Occasionally hyperpigmented scaling pellagrous like

rhosis of the liver, prolonged febrile illness, diarrheal diseases, diabetes mellitus and neoplasia often develop signs of niacin inadequacy Prolonged parenteral feeding without niacin supplementation has led to acute pellagra

VITAMIN B_6

Although vitamin B_6 has been shown only recently to be essential in human nutrition, much information has accumulated as to its important role in metabolic processes Vitamin B_6 comprises a group of three closely related compounds, pyridoxine, pyridoxal and pyridoxamine Pyridoxal phosphate functions as a coenzyme in a number of reactions involving amino acids, namely, decarboxylation, transamination and desulfuration (101) Through these reactions, materials are provided for the Krebs cycle, which is one of the important energy sources of the body new amino acids are formed and sulfhydryl groups are transferred from one compound to another Vitamin B_6 has a role in tryptophan metabolism in the conversion of tryptophan to niacin derivatives and functions in the interconversion of essential fatty acids The exact requirement of vitamin B_6 has not been determined but available evidence suggests that 1 0 to 2 0 mg daily should be sufficient for an adult, an amount easily provided by the average diet in the United States

Vitamin B_6 Deficiency

Vitamin B_6 deficiency was induced experimentally in two infants both of whom ceased gaining weight while one developed convulsions and the other hypochromic anemia (102) Pyridoxic acid, the main excretory product of pyridoxine metabolism, disappeared from the urine and the ability to convert tryptophan to niacin was lost A syndrome apparently due to vitamin B_6 deficiency was

pyridoxine administration In some instances, xanthurenic acid excretion after tryptophan administration was abnormally high prior to treatment and decreased following pyridoxine administration Pyridoxine has been used in the treatment of cheilosis, the lesions healing in some subjects In seborrheic dermatitis of the secca type, application of an ointment containing pyridoxine, but not oral administration of the vitamin, resulted in improvement in lesions in one series of subjects but not in another (101)

Although dietary deficiency of pyridoxine is an unlikely possibility, it seems logical to anticipate that deficiency may occur in numerous situations in which metabolism is deranged The appearance of some of the clinical manifestations enumerated above should stimulate diagnostic studies to evaluate pyridoxine nutrition Two laboratory procedures are available which measure metabolic functions of pyridoxine Administration of a large dose 10 0 gm of dl tryptophan stresses the enzyme systems responsible for its degradation Normal subjects will excrete less than 50 0 mg of xanthurenic acid in the urine in the 24 hours after this test dose while subjects with deficiency will excrete larger amounts The second procedure is determination of the concentration of blood urea nitrogen after administration of 30 0 gm of alanine The concentration should return to normal within twelve hours if pyridoxine is available in adequate amounts

PANTOTHENIC ACID

Demonstration that pantothenic acid is essential in animal nutrition and elucidation of its vital role in metabolic processes makes it practically certain that this vitamin is essential in man Pantothenic acid is a constitutent of coenzyme A which occupies a central position

dermatitis developed on the arms and legs Cheilosis, glossitis, angular stomatitis, peripheral neuritis and con junctivitis were noted in some subjects These lesions, many of which resemble those of riboflavin, thiamine or niacin deficiency healed only after pyridoxine was ad ministered Lymphopenia occurred regularly in these subjects The excretion of xanthurenic acid in the urine after administration of a test dose of tryptophan was markedly increased but the conversion of tryptophan to niacin was unimpaired Abnormally high levels of blood urea nitrogen were observed after administration of alanine

Several studies indicate that pyridoxine metabolism may be altered during pregnancy (106) Lower levels of urea nitrogen in the blood were found in pregnant than in nonpregnant women and concentrations were still further reduced in hyperemesis gravidarum When the amino acid alanine was administered, blood urea nitrogen concentration remained elevated for more than 12 hours (106a) Similar findings have been reported in vitamin B_6 deficiency in animals Pregnant women have been found to excrete abnormally large amounts of xan thurenic acid after administration of tryptophan the ab normality being corrected by pyridoxine (106b) These findings suggest that pyridoxine requirement may be in creased during pregnancy

Large amounts of pyridoxine have been shown to prevent or alleviate the peripheral neuritis which may develop during therapy with isoniazid (101) It has been hypothesized that isoniazid may couple with pyridoxal to form pyridoxal isoniazid hydrozone thus inactivating enzyme systems dependent on pyridoxal In this way, a conditioned vitamin B_6 deficiency might be induced The peripheral neuritis which has been observed in some subjects with chronic alcoholism has improved following

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in metabolism This coenzyme is required for acetylation reactions It functions in the synthesis and degradation of fatty acids and in the entry of fat and carbohydrate into the citric acid cycle Coenzyme A functions in the synthesis of the porphyrin part of the hemoglobin molecule and in the formation of sterols and steriod hormones

The wide distribution of pantothenic acid in foods may explain failure to observe deficiency even on severely restricted diets Bean and associates (107) investigated the effects of a pantothenic acid free diet, to which the pantothenic acid antagonist, omegamethyl pantothenic acid was added, in four human subjects A number of physical and biochemical disturbances resulted, most of which appeared to be due to pantothenic acid deficiency The subjects became quarrelsome, sullen, petulant and at times, somnolent Paraesthesias of the hands and feet were followed by the appearance of hyperactive reflexes, steppage gait and foot drop Other findings were cardiovascular instability, especially in the upright position, gastrointestinal complaints and repeated infections Biochemical changes included alterations in acetylation, carbohydrate metabolism serum cholesterol concentration plasma proteins steroid hormone excretion and failure of corticotropin (ACTH) to induce eosinopenia Plasma ascorbic acid concentration decreased while urinary excretion of thiamine and niacin rose during the period of pantothenic acid depletion Individual variations in response to the regimen were large

This study strongly suggests the essentiality of pantothenic acid in human nutrition Bean and associates suggest also that 'burning feet' a complaint of naturally occurring deficiency states, may be mediated by pantothenic acid deficiency Gopalan (108) has reported relief of the burning foot syndrome with pantothenic acid In

other studies, pantothenic acid has been reported to influence the reaction of human subjects to stress (109) Evaluation of pantothenic acid nutrition must await further investigation and the development and testing of procedures which will indicate metabolic defects due to deficiency of this vitamin

FOLIC ACID (FOLACIN - PTEROYLGLUTAMIC ACID)

The folic acid group of substances has been shown to be essential for blood formation in man, presumably it is necessary for other important functions as demonstrated in several animal species Macrocytic anemia which responds to folic acid has been observed in infancy, during pregnancy, in sprue and other malabsorption syndromes, in association with poor diets (nutritional macrocytic anemia) and in other less common conditions such as intestinal stricture or following operative procedures in which the intestinal tract was short circuited (110)

Folic acid is present in foods in both free and conjugated forms, namely, as pteroylglutamic acid, pteroyltriglutamic acid and pteroylheptaglutamic acid Another member of the folic acid group of substances, folinic acid or citrovorum factor, a formyltetrahydro derivative of folic acid is also found in natural materials in free and combined form This compound is also formed in the body from folic acid and is excreted in the urine Information concerning the amounts of the various folic acid compounds in foods and their biological availability is meagre The best sources appear to be liver, deep green leafy vegetables, other green vegetables kidney muscle meat and whole wheat cereals Darby (111) has reported that diets adequate in other respects furnish about 0 1 to 0 4 mg of folic acid compounds daily, poor diets less than 0 1 mg

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aloblastic bone marrow appear to be primarily syndromes of folic acid deficiency, namely, the macrocytic anemia of pregnancy and the megaloblastic anemia of infancy Nutritional macrocytic anemia and sprue also appear to be due to deficiency of folic acid in some instances while in others, deficiency of Vitamin B_{12} or both factors may be present. The megaloblastic anemia associated with intestinal stricture or anastomosis and, at times, the macrocytic anemia which occurs in primary liver disease responds to folic acid therapy (113)

Clinical findings common to both sprue and nutritional macrocytic anemia are the history of an inadequate diet, glossitis, diarrhea, loss of weight and impaired absorption from the gastrointestional tract. In both conditions, a flat glucose intolerance test is a frequent finding Steatorrhea is characteristic of sprue, the stools containing large amounts of fatty acids but little neutral fat. Absorption of fat and of fat soluble vitamins is impaired This may be demonstrated by administration of fat or of oily preparations of vitamin A and measuring the respective blood levels at intervals thereafter (p 59) Tetany due to hypocalcemia may occur in sprue due to the combination of fatty acids and calcium in the intestinal tract to form insoluble soaps Recent studies in our laboratory indicate that so-called nutritional macrocytic anemia is, in many instances a malabsorption syndrome glucose, fat and vitamin B_{12} (even when combined with intrinsic factor) are poorly absorbed from the intestinal tract.

Administration of folic acid or citrovorum factor will be followed by hematopoietic response and relief of most of the abnormal findings in sprue and nutrional macrocytic anemia in the majority of subjects In sprue steatorrhea may persist and in both conditions it is at times necessary to continue therapy indefinitely to prevent re-

Folic acid is synthesized by intestinal bacteria and this source of supply may be important in man, since experimental deficiency has not been induced by diets low in folic acid Evidence from studies in animals, and from therapeutic tests in human macrocytic anemia, suggest that the dietary requirement of folic acid is less than 0 2 mg daily

Folic acid participates in the synthesis of compounds which are used in the formation of nucleoproteins and in transmethylation processes It is concerned with incorporation of the "single carbon unit" into the 2 and 8 positions of the purine ring and the 5 methyl group of thymine and with some of the reactions relating to the formation of choline, creatine and histidine (112) Folic acid is essential for maintenance of normal hematopoiesis, exerting a hematologic effect in practically all types of human macrocytic anemia, presumably by its function in the formation of thymine and other purines and pyrimidines Although folic acid stimulates blood regeneration in pernicious anemia neurologic lesions are unaffected and hematologic relapse occurs unless vitamin B_{12} is administered

Folic Acid Deficiency

The syndrome of folic acid deficiency is exemplified by the toxic symptoms which develop during administration of aminopterin a folic acid antagonist (110) These symptoms include glossitis, diarrhea gastrointestinal lesions and anemia Toxic manifestations of aminopterin may be reversed by citrovorum factor, if administered promptly but not by folic acid Presumably aminopterin interferes with the conversion of folic acid to its metabolically active form

Several types of human macrocytic anemia with meg-

tionships of folic acid, vitamin B_{12} and ascorbic acid in patients with megaloblastic anemia have been discussed in detail by Mueller and Will (116)

Other metabolic relationships between folic acid and ascorbic acid have been reported Abnormal excretion of tyrosine metabolites occurs in infants with scurvy and in premature infants given a diet which furnishes large amounts of tyrosine This abnormal excretion may be prevented or relieved by administration of ascorbic acid or by large doses of folic acid (118) There is some evidence that ascorbic acid assists in the conversion of folic acid to citrovorum factor or in the release of citrovorum factor from conjugated form (110, 112)

The pathogenesis of nutritional macrocytic anemia and sprue is not clear Neither appears to be due solely to dietary deficiency of folic acid of vitamin B_{12} or of both factors In some instances, inflammatory disease of the intestinal tract precedes the development of the sprue syndrome and could be responsible for defective absorption but this is not always the case In some subjects with so called nutritional macrocytic anemia, relapse occurs when therapy with folic acid or vitamin B_{12} is discontinued even though an adequate diet is ingested As noted previously some of these subjects have defects in absorption which may be permanent others may have increased requirement and/or abnormal utilization of the anti anemic vitamins Some subjects may be deficient in intrinsic factor as are patients with pernicious anemia

Laboratory tests have been developed which permit measurement of folic acid concentration in blood and excretion of folic acid and citrovorum factor in the urine In normal subjects receiving ordinary diets average excretion was reported to be 4 1 and 2 6 micrograms daily for folic acid and citrovorum factor, respectively (119)

lapse In some instances, vitamin B_{12} is as effective as folic acid in the therapy of these diseases and occasionally the two vitamins are more beneficial when given together than is either one alone

It is interesting to speculate as to the mechanism which leads to folic acid deficiency in the diverse syndromes mentioned above In several animal species, folic acid has been shown to have a role in the reproductive process (113) It was reported recently that administration of a folic acid antagonist, 4 amino pteroylglutamic acid to 12 women who were less than three months pregnant was followed by abortion in ten instances (114) Perhaps there is an increased need of folic acid during pregnancy which is not always met by the dietary intake In such instances, macrocytic anemia might ensue

Megaloblastic anemia of infancy presents a complex problem, it appears to be related to deficiency of ascorbic acid as well as of folic acid (112) In the United States this anemia was observed chiefly in infants who received a powdered milk preparation low in vitamin C and has been encountered only rarely since ascorbic acid was added to the formula of this product The anemia occurs in the same age group in which the incidence of scurvy is high Megaloblastic anemia of infancy responds to folic acid or citrovorum factor but not to ascorbic acid May and associates (117) produced an anemia in monkeys, comparable to that seen in infants by administration of a diet *deficient in both ascorbic and folic acid* The anemia could be prevented by ascorbic acid alone but responded only partially to treatment with this vitamin Therapy with folic acid was completely satisfactory

In South Africa megaloblastic anemia has been encountered in adults with severe scurvy although it is rare (115) This anemia responds to ascorbic acid Interrela

vitamin B_{12} is nitritocobalamin An interesting facet of the metabolism of vitamin B_{12} is its dependence for absorption, in the amounts present in the diet, on the intrinsic factor of gastric juice Accordingly, pernicious anemia, which is due to deficiency of vitamin B_{12}, does not develop because of dietary inadequacy but because of an insufficient supply of intrinsic factor It is also of interest that when very large amounts of vitamin B_{12} are administered orally, absorption occurs in the absence of intrinsic factor (123)

In spite of extensive investigation the chemical structure of intrinsic factor is unknown and the mechanism by which it influences absorption has not been elucidated (124) A number of modes of action have been suggested (125) An attractive postulate is that absorption is regulated by a mechanism similar to that for the absorption of iron (126) Intrinsic factor may have functions other than facilitating absorption of vitamin B_{12} It is known that most of the vitamin B_{12} in blood is bound to the alpha and beta globulin fractions of serum protein, very little is present as the free vitamin Recent studies suggest that intrinsic factor may facilitate the combination of vitamin B_{12} with a specific protein moiety of serum (127) Miller and associates (128) have found that intrinsic factor concentrates from hog intestine stimulate the uptake of vitamin B_{12} by liver slices or homogenates and also by homogenates of kidney and intestinal mucosa Other studies in our laboratory indicate that there may be a deficiency of the protein factor in serum which combines with vitamin B_{12} in some patients with macrocytic anemia (129) These observations may lead to a better understanding of the pathologic physiology of pernicious anemia and should assist in the development of new tests useful in diagnosis (p 131)

Some reports indicate that patients with pernicious anemia and sprue excrete smaller amounts of folic acid and citrovorum factor after a test dose of folic acid than do normal subjects (120) Girdwood (120b) has suggested that an excretion of less than 1 5 mg in 24 hours after an oral test dose of 5 0 mg of folic acid is indicative of either severe tissue depletion or malabsorption If tissues have been loaded with folic acid prior to testing a small excretion after an oral, as compared to a par enteral, test dose is indicative of malabsorption Few studies of levels of folic acid in blood have been carried out None of these procedures has been studied exten sively in the evaluation of folic acid nutrition

VITAMIN B_1 (COBALAMIN)

The isolation of vitamin B_{12} and the demonstration that this substance is the anti pernicious anemia factor of liver was an outstanding achievement (121) Search for this factor had been continuous since the late 1920s when Minot and Murphy demonstrated the efficacy of liver in the treatment of pernicious anemia and Castle proposed his theory of the pathogenesis of this disease Castle postulated that an intrinsic factor in gastric juice com bined with an extrinsic factor in food to form the anti pernicious anemia factor of liver Intrinsic factor was found to be absent from the gastric juice of patients with pernicious anemia It is now known that vitamin B_{12} is not only the antipernicious anemia factor of liver but is also the extrinsic factor of food (122)

Vitamin B_1 like many other members of the B complex, is not a single substance but comprises a group of closely related compounds with similar physiologic activity Vitamin B_{12} itself is cyanocobalamin while vitamin B_1 $_{b\ and\ d}$ which are identical are hydroxycobalamin and

findings Neurologic abnormalities are common, particularly parasthesias of the fingers and toes and signs of peripheral neuritis or subacute combined degeneration of the spinal cord Gastrointestinal complaints are frequent and glossitis is observed in most instances

The peripheral blood shows severe macrocytic anemia, leukopenia with hypersegmentation of the polymorphonuclear cells, and thrombocytopenia The bone marrow is hyperplastic and contains large numbers of megaloblasts Excessive erythrocyte destruction is manfested by an increase in the concentration of bilirubin in serum and high urobilin excretion in the urine Hydrochloric acid is absent from the gastric juice even after stimulation with histamine An abnormality of tyrosine metabolism is demonstrated by the excretion of certain phenolic compounds in the urine

While diagnosis is easy in the classical case of pernicious anemia, difficulties often arise in differentiation from sprue and nutritional macrocytic anemia and even from macrocytic anemia in diseases unrelated to nutritional deficiency Estimation of the concentration of vitamin B_{12} in serum is of considerable value in diagnosis and in judging the adequacy of therapy (123b, 30) The concentration of vitamin B_{12} in serum falls to abnormally low levels in pernicious anemia in relapse even before there is significant decrease in erythrocytes in the peripheral blood The level returns to normal with therapy The exact concentration indicative of pernicious anemia is dependent on the method of assay which is employed With a microbiological assay using *L Leichmanii* as the test organism (131), normal serum contains from 80 to about 500 micromicrograms ($\mu\mu g$) per milliliter In pernicious anemia serum concentration is below the normal range and in some instances no vitamin B_{12}

Vitamin B_{12} is undoubtedly an essential human nutrient but present information is insufficient to estimate dietary requirement The administration of approximately 1 microgram daily, parenterally, will induce remission in pernicious anemia (4a) Presumably, the normal adult needs to absorb an amount no larger than this but the biological availability of vitamin B_{12} in the diet remains unknown Vitamin B_{12} is required for growth in animals Studies of the effect of vitamin B_{12} on growth in human subjects have been equivocal (113) It seems likely that under certain conditions of diet and nutrition, vitamin B_{12} may have a growth promoting effect

The metabolic functions of vitamin B_{12} are gradually being elucidated (125) This vitamin appears to be involved in the synthesis of nucleoproteins by way of its participation in the metabolism of purines and pyrimidines Promotion of normal hematopoiesis may be explained on this basis The mode of action in the metabolism of nervous tissue has not been clarified Vitamin B_{12} may have a role in the metabolism of methyl, hydroxy methyl and sulfhydryl groups

Vitamin B_{12} Deficiency

From the clinical standpoint vitamin B_{12} deficiency is seen primarily in pernicious anemia Several other types of macrocytic anemia and some neurologic disorders may also be due to deficiency of this vitamin Until recently the diagnosis of pernicious anemia has been dependent entirely on clinical and nonspecific laboratory findings Characteristically the disease occurs in well nourished persons of middle age or beyond who give a history of similar illness in other members of the family Weakness lemon yellow pallor of the skin and signs of cerebral anoxemia or congestive heart failure are often presenting

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can be detected. Normal levels of serum vitamin B_{12} assayed with the organism *Euglena gracilis* range from 350 to 750 micromicrograms per milliliter (132). Low levels of vitamin B_{12} in blood may be observed in macrocytic anemias other than pernicious anemia that will respond to vitamin B_{12}.

The urinary excretion of vitamin B_{12} has been studied by numerous investigators (110). Register and Sarett (119) found an average excretion of 31 millimicrograms (mμg) daily in normal subjects on ordinary diets. In other studies, somewhat higher values have been reported. Excretion tends to be less in patients with pernicious anemia than in normal persons but large variation among individuals prevents this test from being of diagnostic value. Studies of urinary excretion following parenteral injection of vitamin B_{12} indicate, in general, an increase in excretion with increasing dosage (123b). Following oral administration of vitamin B_{12} there is little increase in urinary excretion unless very large doses (1.0 to 3.0 mg.) are administered. Even in these instances excretion is less than anticipated by the concentration of vitamin B_{12} in serum, i.e. at levels comparable to those obtained with parenteral doses, urinary excretion is much lower.

A procedure which has been developed for indirectly detecting the presence or absence of intrinsic factor in the gastric juice is the Schilling test (133) which employs vitamin B_{12} labeled with an isotope of cobalt, Co^{60}. Two micrograms of the vitamin (0.5 microcuries radioactivity) is administered orally followed in 2 hours by a 1000 μg parenteral "flushing" dose of non labeled vitamin. Urine is collected for 24 hours and radioactivity measured. In our experience, normal subjects usually excrete more than 6% of the radioactive vitamin with this tech

nique whereas patients with pernicious anemia excrete less than 2%, the amount often being barely detectable The test is repeated after two or three days using a similar oral dose of Co_{60} vitamin B_{12} combined with intrinsic factor Excretion of vitamin B_{12} will increase to normal levels in patients with pernicious anemia In sprue and other macrocytic anemias in which intestinal absorption is defective, excretion remains low even in the presence of intrinsic factor

Other tests of absorption of vitamin B_{12} include measurement of radioactivity in the feces after oral administration of Co^{60} vitamin B_{12} (134) and comparison of radioactivity over the liver after oral and parenteral administration of the labeled vitamin (126)

An *in vitro* test for intrinsic factor activity which may be applied to gastric juice has been developed in our laboratory (127) It is dependent upon the ability of intrinsic factor to increase the amount of vitamin B_{12} which will combine with serum proteins A procedure for measuring "serum factor" in blood, i e, the protein moiety which binds vitamin B_{12} has also been developed Patients with pernicious anemia show low intrinsic factor activity in gastric juice and often low "serum factor" with these procedures In some subjects with so called nutritional macrocytic anemia both tests are extremely low Further study with these procedures may assist in elucidating the etiology of some of the macrocytic anemias and be helpful in their differentiation

Vitamin B_{12} has been found to be effective therapeutically in several types of macrocytic anemia other than pernicious anemia, including that which follows gastrectomy the anemia associated with fish tapeworm infestation, some instances of sprue and nutritional macrocytic anemia and rarely, in macrocytic anemia of chronic liver

disease Following total gastrectomy, vitamin B_{12} deficiency develops on the same basis as in pernicious anemia, that is, absence of intrinsic factor Vitamin B_{12} deficiency in sprue and nutritional macrocytic anemia may be due to dietary deficiency, impaired absorption, deficiency of serum factor or some other cause as yet unappreciated The macrocytic anemia of fish tapeworm infestation appears to be due to utilization of vitamin B_{12} by the parasite in the intestinal tract In cirrhosis of the liver, storage of vitamin B_{12} may be impaired

Vitamin B_1 has been used in the treatment of a number of neurologic diseases unassociated with pernicious anemia This vitamin has been reported to relieve the pain of nutritional neuropathy (135) and to be beneficial, at times, in the therapy of peripheral neuritis associated with diabetes mellitus (136) In our experience, vitamin B_{12} has been efficacious in some instances in treating neuritis that occurred in subjects who had chronic alcoholism and cirrhosis of the liver Whether a deficiency of vitamin B_1 is present in these conditions remains unknown Some abnormality of utilization rather than dietary inadequacy might explain the findings Massive parenteral doses of vitamin B_{12}, 1000 μg daily, have been reported to be followed by cessation of pain in trigeminal neuralgia (137) In this situation, vitamin B_{12} may be exerting a pharmacologic rather than a physiologic action

CHOLINE

Little is known about the importance of choline in human nutrition nor are methods available for the diagnosis of choline deficiency In animal experiments administration of diets low in choline leads to deficiency which is characterized by accumulation of fat in the liver and hemorrhagic lesions of the kidney Choline func-

tions as an integral part of acetylcholine, as a source of labile methyl groups and in the formation of phospholipids The dietary requirement of choline in animals or man is uncertain since this compound can be manufactured in the body and the need is dependent on other sources of methyl groups in the diet, such as methionine or betaine Elvehjem (138) suggested on the basis of animal studies that the human requirement is probably less than 500 mg daily The average diet contains about 250 to 600 mg of choline

Choline has been reported to be beneficial in the treatment of fatty liver and cirrhosis in man It is difficult to evaluate such therapy since administration of choline has usually been only one aspect of a regimen which has included a diet high in protein and, in some instances administration of methionine Cornatzer and Cayer (39) found that the administration of a single 10 0 gm dose of choline resulted in an increase in the rate of phospholipid turnover in subjects in whom fatty infiltration of the liver was demonstrated on initial biopsy When fat was not present in the liver, this effect was not observed Eckhardt and associates (39) in an investigation of subjects with active fatty alcoholic cirrhosis, reported that choline administration was followed by a moderate reduction in liver fat as seen in biopsy specimens The liver cell showed much greater improvement however when a diet adequate in protein was prescribed

Choline methionine vitamin B_{12} and folic acid have been found to be interrelated in the prevention of fatty livers under certain dietary conditions in animals Whether these findings are applicable to man is unknown

BIOTIN

It seems most unlikely that spontaneous biotin deficiency will be observed in human subjects Although biotin is presumably an essential nutrient, not only is it present in food but it is synthesized by the intestinal flora The amounts of biotin excreted in the urine and in the feces are greater than the intake Current knowledge of the metabolism of biotin has been reviewed by Wright (140) Biotin is the anti egg white injury factor, raw egg white contains avidin which combines with biotin making it unavailable to the body Sydenstricker and associates (141) produced experimental human deficiency by feeding large amounts of raw egg-white Manifestations included anorexia, muscle pains, and dry scaly dermatitis

INOSITOL

Little is known of the role of inositol in the nutrition of animals or man Inositol has been administered in conjunction with other agents, in the therapy of several pathologic states for example, chronic liver disease and muscular dystrophy, on postulates which have little factual support The value of inositol in such situations remains unproved

ASCORBIC ACID

Scurvy was described with accuracy several centuries ago and satisfactory treatment was devised long before ascorbic acid was isolated Only recently however has a role for ascorbic acid in conditions other than scurvy been suggested Extensive investigation has indicated the many biologic functions of this vitamin but its chemical action in metabolic processes remains unclear

In evaluating dietary intake of ascorbic acid it should be remembered that this water-soluble vitamin is easily

oxidized and that loss in the storage and preparation of food may be great The vitamin may be destroyed in the upper intestinal tract in subjects who have achlorhydria or who have received alkaline medication The minimal amount of ascorbic acid which will prevent scurvy is about 10 0 mg daily The amount which should be recommended for the maintenance of good nutrition is a subject of controversy The allowances suggested in this country are given in Table 3 It is believed by proponents of other dietary standards that smaller quantities will suffice (4b 4c)

In ascorbic acid deficiency, connective tissue is defective presumably due to the essentiality of this vitamin for the production of collagen (142) The changes in bones teeth and gums which occur in scurvy and the poor healing of wounds, are believed to be secondary to this fundamental defect The hemorrhagic phenomena represent a capillary defect due perhaps to abnormal pericapillary connective tissue

One metabolic function of ascorbic acid has been elucidated recently it acts as a coenzyme in the oxidation of tyrosine (143) This finding explains the abnormal excretion of tyrosine metabolites in scurvy and the return to normal after ascorbic acid has been administered Folic acid will also correct this metabolic defect (p 125)

Relationships of ascorbic acid to adrenal cortical function have been investigated extensively (144) Stimulation of the adrenal cortex leads to depletion of ascorbic acid stores in the gland but cortical function is maintained even in severe depletion Investigations using ascorbic acid and acetate labeled with C^{14} indicate that the vitamin exerts an effect on the conversion of acetate to cholesterol and other steroids (145) Ascorbic acid has been reported to prevent the alarm reaction of acute

stress in experimental animals While much remains to be learned about the function of ascorbic acid in the adrenal cortex, available evidence suggests an increased utilization and requirement of ascorbic acid under conditions of stress It seems advisable therefore to administer ascorbic acid in chronic stress states, particularly following burns or other trauma and during prolonged administration of corticotropin

The ascorbic acid requirement appears to be increased in hyperthyroidism Plasma ascorbic acid decreases in a number of infections, particularly those of long duration such as tuberculosis or rheumatic fever Whether this decrease represents an increase in ascorbic acid requirement or a redistribution of the vitamin in the body is not clear Although the role of ascorbic acid in infection is not known, it would seem logical to supplement the diet with this vitamin when infections are prolonged

Ascorbic acid has a number of biologic functions in addition to those discussed above such as an influence on the hyaluronidase hyaluronic acid reaction an effect on the reaction of small blood vessels to adrenaline and some relationship to secretion of steroid hormones in the ovary (146) Many of the activities of this vitamin suggest that it may function as a respiratory catalyst but to date this has not been demonstrated

Ascorbic Acid Deficiency

Ascorbic acid deficiency has been induced experimentally in adults on several occasions (147) Clinical signs of deficiency included hyperkeratotic papules surrounding hair follicles, exacerbation of acne, perifollicular hemorrhages and petechiae, small hemorrhages in the tips of the interdental papillae and poor wound healing The gums became purplish, spongy and swollen in sub-

jects who had previously shown periodontal disease and interruptions of the laminal dura were noted in x ray films of the teeth In spontaneous scurvy in adults findings similar to those noted above are observed When deficiency becomes severe, bleeding may occur into any tissue of the body or from any mucous membrane Swelling of joints, edema and anemia are additional findings The gums may be very red, swollen and bleed on slight pressure loosening of the teeth and atrophy of alveolar bone may occur Anemia is common in severe scurvy in adults and responds to ascorbic acid (115)

In infants, the majority of cases of scurvy occur between the ages of 7 and 11 months The most frequent presenting complaints according to Woodruff (143) are irritability, tenderness of the legs and pseudoparalysis, i e failure to move or use the legs Involvement of the arms is less common A history of bleeding or its manifestation is another frequent presenting symptom Non specific complaints often noted are anorexia diarrhea and fever In typical scurvy the infant lies quietly in the pithed frog" position with legs flexed at the knees and hips flexed and externally rotated The slightest jarring or motion causes crying due to the pain which is invoked Costochondral beading the most frequent physical finding in Woodruff's series of cases may cause confusion with rickets Beading in scurvy is typically "sharp" consisting of subluxation of the cartilaginous portion of the anterior chest wall on the bony lateral portion producing an abrupt transition the so called bayonet deformity However, a rounded type of beading similar to rickets may be encountered Hemorrhage around erupting teeth is a constant finding with bleeding after manipulation in advanced cases Palpable subperiosteal hemorrhages are frequent particularly in the distal end

of the femur and proximal end of the tibia Bleeding may occur from any of the mucous membranes although hemorrhages into the skin are relatively uncommon, in contrast to scurvy in adults

Radiographic examination of the long bones shows characteristic changes at the cartilage-shaft junction appearing earliest at the sites of most active growth, e g, the sternal ends of the ribs, distal end of the femur, proximal end of the humerus, both ends of the tibia and fibula and distal ends of the radius and ulna Findings include cortical atrophy, the cortex being unusually thin *in relation to the shaft,* and atrophy of the trabecular structure with increased transparency producing a ground glass appearance The provisional zone of calcification at the end of the shaft is widened casting a dense shadow, similar changes occur in the periphery of ossification centers, best illustrated about the knee (148) This latter change, in conjunction with rarefaction and loss of trabecular markings in the epiphyseal center, is almost specific for scurvy A zone of rarefaction is visible shaftward from the zone of provisional calcification being apparent first near the cortex this plus the extremely thin cortex constitute the corner sign or fracture described by Park This area of rarefaction is weak and fractures may occur here and also in the brittle zone of provisional calcification Comminution of the latter zone into the shaft causes the appearance of spur formation Separation of the epiphysis with lateral displacement may occur Shadows of subperiosteal hemorrhages are also seen on the roentgenogram the area of hemorrhage becoming clearly outlined by bone formation in the periosteum after several days of treatment Following therapy, the normal architecture of the bone is fully restored

Anemia is quite common in infantile scurvy usually

being hypochromic and due to iron deficiency Occasionally megaloblastic anemia is encountered (p 124) The leukocyte count is often elevated except in subjects with megaloblastic changes in the bone marrow There is an increased output of tyrosine metabolites in the urine when large amounts of this amino acid are ingested

The diagnosis of scurvy in infants or adults is dependent on a history of extremely low intake of ascorbic acid for a period of months, at least three in infancy and longer in adults, the presence of symptoms which suggest the disease and characteristic physical findings In infants, radiologic changes are of great assistance

The diagnosis of ascorbic acid deficiency in its incipiency is dependent on laboratory tests The concentration of ascorbic acid in the plasma reflects dietary intake In adults, levels of 0.6 to 1 mg/100 ml indicate a daily intake of 70 mg or more, levels of less than 0.2 mg/100 ml an intake of less than 25 mg (17) Unfortunately, low concentrations do not indicate the degree of depletion of bodily stores of ascorbic acid and absence of ascorbic acid in plasma does not indicate scurvy When such levels are encountered, the ascorbic acid content of the white cell platelet layer of blood should be measured Concentrations of ascorbic acid in leukocytes below 2 mg/100 ml should be considered presumptive evidence of scurvy In well nourished adults receiving 70 to 100 mg of ascorbic acid daily, the level of ascorbic acid in white blood cells is 20-30 mg/100 ml

Some type of "load" test may also be used in evaluating ascorbic acid stores of the body The vitamin may be administered orally or intravenously and the urinary excretion or concentration in the blood measured for several hours thereafter These tests and others involving urinary excretion of ascorbic acid have been evaluated in a recent

review (17) Woodruff employed the saturation test of Kadji and associates to differentiate scorbutic infants from infants with no ascorbic acid in serum as a result of a poor recent diet In this procedure, 200 mg of ascorbic acid is administered intramuscularly and serum concentration determined four hours thereafter In practically all infants with scurvy, the four hour level was less than 0 4 mg/100 ml and in about half of the subjects this level was zero

Lowry (17) has proposed a test for measuring tissue deficit under carefully controlled conditions Ascorbic acid is administered in amounts of 500 2000 mg daily, in divided doses to avoid raising the plasma level above 1 4 mg/100 ml which is the renal threshold and the quantity of the vitamin excreted in the urine is determined Tissue retention should equal tissue deficit when suitable correction is made for destruction of the vitamin

Capillary fragility tests which have been widely used are of almost no value in the diagnosis of ascorbic acid deficiency in view of the many conditions which influence capillary strength

VITAMIN D

Vitamin D deficiency is rarely observed in adults and is becoming uncommon in infants due to the widespread use of dietary supplements in the early months of life A unique feature of vitamin D metabolism is the formation of this vitamin in the skin on exposure to sunlight or ultraviolet rays and consequently only partial dependence of the body on a dietary supply Actually only small amounts of vitamin D are present in the average diet

In several animal species the susceptibility to rickets is influenced by dietary changes such as the inclusion of cereals containing phytic acid which decreases absorption

of calcium Phytate also appears to interfere with the absorption of calcium in man (149) Since vitamin D is fat soluble, absorption is impaired in conditions asso ciated with decreased absorption of fats as when bile is absent from the intestinal tract or in the steatorrheas

Vitamin D consists of a group of sterol derivatives in cluding vitamin D activated ergosterol, which is derived from plants and vitamin D_3 activated dehydrocholesterol, which is found in animal tissues Vitamin D is measured in International Units, one unit being equivalent to the activity of 0 025 μg of calciferol (crystalline vitamine D_2) In infancy, maximum retention of calcium will be attained with administration of 300 - 400 I U of vitamin D daily if the diet contains an ample supply of calcium and phos phorus (150) Larger amounts of vitamin D are not beneficial and a daily dose of more than 1800 I U may be deleterious Maximum retention of calcium is associated with good skeletal growth and early dentition The ma jority of children probably require supplementary vitamin D throughout the period of growth and practically all need it during adolescence The recommended allowance for vitamin D is 400 I U daily from birth to 20 years of age (Table 3)

Supplements of vitamin D would seem desirable during pregnancy and lactation in view of the increased need of calcium and phosphorus in these conditions In adults the need for supplemental vitamin D appears to be minimal except in unusual circumstances in which occupation or habits prevent exposure to sunlight

Vitamin D functions by increasing absorption of calcium from the intestinal tract, possibly increasing the absorption of phosphorus as well and decreasing the urinary excretion of phosphorus by enhancing reabsorption in the renal tubule The renal influence may be due in

part, to diminished activity of the parathyroid glands which follows a rise in serum calcium induced by vitamin D In addition to maintaining levels of calcium and phosphorus in blood which are suitable for deposition of bone, vitamin D is believed to exert some direct effect at the site of bone formation Recent investigation suggests that vitamin D may activate alkaline phosphatases of bone, kidney and intestine but this enzymatic role of the vitamin needs confirmation Normal bone formation requires an adequate supply of calcium and phosphorus as well as vitamin D

Vitamin D Deficiency

Vitamin D deficiency is characterized by poor retention of calcium and phosphorus and retarded skeletal growth, particularly in infancy and early childhood, and by osteomalacia in adult life The clinical signs of rickets vary greatly depending on the severity of the process and on the age rate of growth and stage of physical development when the disease is active The earliest findings are deformities of the skeleton which have been described so well by Park (151) Craniotabes which may be seen as early as the second month, consists of areas of softening of the skull usually involving the occipital and parietal bones along the lambdoidal suture The anterior fontanel does not close at the usual time and the margins are soft, as are the margins of the cranial bones that form the sutures In severe rickets the skull can become very thick particularly at the frontal and parietal eminences resulting in the so-called rachitic "bossing" of the skull Thickening may occur concomitantly with thinning and craniotabes in the back of the skull

Another early sign of rickets is enlargement of the costochondral junctions often referred to as beading of the

ribs or the rachitic rosary Other deformities of the thorax include pigeon breast and Harrison s grooves The latter are depressions at the sides of the chest at the level of the diaphragmatic attachments which develop as a result of muscle pull Abdominal distention commonly accompanies rickets and accentuates these grooves

The rachitic child shows postural kyphosis on sitting and lordosis on standing The long bones become enlarged at the ends, most readily seen at the wrists and ankles The shafts of the bones may be curved the direction of curvature being dependent on the age at which rickets occurs Anterior bowing of the tibia or "saber shin" occurs before weight bearing while lateral deformity, bow legs and knock knees, develop following standing and walking The waddling gait in severe rickets is due to a twist in the tibia and femur (151) Narrowing of the pelvic outlet may occur but injury is rarely permanent except in rickets of long duration

Primary dentition is delayed in rickets and the permanent teeth may show serious defects in enamel formation The muscles are hypotonic and motor development is delayed, the child is slow in sitting and walking This muscular relaxation is also responsible for the pot belly Tetany due to low serum calcium concentration may complicate the clinical picture of rickets

Roentgenographic examination of the bones will reveal abnormalities except in early rickets and healing may be followed by serial roentgenograms Characteristic changes are observed at the cartilage-shaft junctions and in the shafts of the long bones (151) The end of the shaft appears cupped in the x ray first visible at both ends of the fibula and the lower end of the ulna, later in the ends of the tibia and the lower ends of the radius and

femur Cupping occurs also in scurvy and in chon drodystrophy

Spreading of the end of the shaft is another common finding in rickets as is fringing which appears as thread like shadows extending from the end of the shaft into the transparent cartilage The end of the shaft may have an irregular dotted or stippled appearance The trabecular network of the shaft becomes coarse and there is a marked decrease in bone density in severe rickets In advanced stages of the disease, the cortex may be thin or non visible or it may be thickened and appear reduplicated Curva tures of the bones are another characteristic finding

In vitamin D deficiency fecal excretion of calcium and phosphorus is increased while urinary excretion of cal cium is decreased and that of phosphorus increased The concentration of inorganic phosphorus in the serum de creases to less than 4 mg/100 ml (2 5 mEq/l) while the concentration of calcium may remain normal or de- crease Determination of alkaline phosphatase in serum is the most important single procedure for diagnosing rickets in its early stages Normal concentration in young children ranges from 5 to 15 Bodansky units Elevation of alkaline phosphatase above 20 units is highly suggestive of rickets since few other conditions influence phos *phatase activity in this age group Such elevation occurs* before clinical rickets is evident Serial determinations of serum phosphatase are useful in following therapy since the return to normal is delayed until healing is complete

Rickets which is refractory to treatment is observed occasionally, especially in children over the age of three The metabolic defect in this condition is not understood, there seems to be interference with the normal calcifying action of vitamin D Massive doses of the vitamin may

promote healing but some of the metabolic abnormalities may not be corrected (152) Relationships between rickets and the Fanconi syndrome have been discussed previously (p 42)

Osteomalacia is an uncommon disease which presumably is the adult counterpart of rickets It occurs most frequently during pregnancy and lactation and is characterized by osteoporosis, deformity and fracture of bones and tetany The first symptom is usually pain in the back and sacral area Muscular weakness is an associated finding which may be pronounced in the adductor muscles of the thighs Stiffness and contractures of the extremities have been reported When deformity develops, it is seen first in the areas in which pain occurs, that is, in the spine and pelvis X ray examination will show extensive demineralization with dislocation and fractures The concentration of serum calcium decreases, often to levels below 7mg/100 ml, (3 5mEq/l) and the level of alkaline serum phosphatase rises above the normal adult value of 3 to 5 Bodansky units Since a number of diseases influence phosphatase concentration in the blood in adults a high level should not be considered evidence of osteomalacia in the absence of other findings

Osteoporosis and tetany may occur in association with sprue the celiac syndrome and idiopathic steatorrhea In these conditions both calcium and vitamin D are poorly absorbed from the intestinal tract

Massive doses of vitamin D given over long periods of time may lead to toxic reactions These include elevation of serum calcium metastatic calcification loss of weight, vomiting and diarrhea Death may occur from renal failure Intoxication may be detected at an early stage by serum calcium determination a rise above 11 5 mg/100 ml (6 m Eq/1) being indicative of excessive dosage

VITAMIN E

Vitamin E has not been shown unequivocally to be essential in human nutrition although evidence suggests that this is the case In experimental animals, manifestations of vitamin E deficiency include fetal resorption and dystrophic changes in skeletal muscle In certain clinical diseases in man which resemble experimental deficiency, namely, habitual abortion and progressive muscular dystrophy, therapy with vitamin E has been attempted Beneficial effects have not been demonstrated in these conditions or in a number of other pathologic states in which vitamin E has been prescribed (153)

An attempt to produce experimental vitamin E deficiency in adult men is under way at present (154) The only abnormal findings after more than three years on a diet very low in vitamin E are a decrease in the concentration of tocopherols in blood and excessive hemolysis of erythrocytes when tested with hydrogen peroxide in vitro It seems unlikely that primary deficiency of vitamin E will occur in healthy adults However, deficiency might arise as a result of impaired absorption, increased requirement or some abnormality in the metabolism of the vitamin

Plasma tocopherol levels have been found to be much lower in infants than in adults Normal levels in the former range from 0 23 to 0 43 mg per 100 ml, in the latter from 1 0 to 1 2 mg per 100 ml (155) Gyorgy and associates (156) observed that erythrocytes of newborn infants were more sensitive to hemolysis by hydrogen peroxide than those of adults and that this sensitivity could be corrected by tocopherol administration Similar sensitivity to hemolysis has been found in premature infants (157) It seems likely that supplementation of the diet of premature infants with tocopherol may be desirable

since fat absorption is defective and both whole cow's milk and stored human milk have limited tocopherol content

Evaluation of vitamin E nutrition must rest, at present, upon determination of plasma tocopherol concentration and the use of the in vitro erythrocyte hemolysis test Absorption of vitamin E may be determined by a tolerance test similar to that described for vitamin A Subjects are given a large dose of tocopherol (5-20 mg per kg body weight) and blood samples taken at 0, 3, 6, 9, 12 and 24 hours Low curves have been reported in sprue, fibrocystic disease of the pancreas, the celiac syndrome and in some but not all cases of liver disease (155) Analysis of tissues specimens, obtained at biopsy, for tocopherol content may prove to be informative

VITAMIN K

Vitamin K is important in human nutrition but deficiency is rarely observed in the absence of some complicating disease except in the infant during the first ten days after birth Vitamin K is present in a large variety of foods and is synthetized by bacteria in the intestinal tract, hence dietary deficiency is an unlikely possibility Deficiency in the first few days of life may be due to inadequate intake during this period or to sterility of the intestinal tract The daily requirement of the infant is approximately 1 0 μg (4a) In the adult, the requirement is unknown but is apparently small and easily supplied by the ordinary diet in addition to the amount available from intestinal synthesis

Since naturally occurring forms of vitamin K are fat soluble, deficiency is observed in a number of diseases in which fat absorption is impaired such as obstructive jaundice biliary fistula, and the steatorrheas sprue the

celiac syndrome, idiopathic steatorrhea and pancreatic fibrosis Poor absorption of vitamin K may lead to deficiency in chronic ulcerative colitis, regional ileitis, other severe diarrheal states and following operative removal or short circuiting of large sections of the intestinal tract Intestinal synthesis of vitamin K may be depressed by prolonged administration of antibiotics

Vitamin K is essential for the formation of prothrombin which is necessary for blood coagulation The precise role of vitamin K in prothrombin formation by the liver is unknown it has been postulated that it may function as the prosthetic group of an enzyme (158) Functions for vitamin K other than involvement in the synthesis of prothrombin have been suggested (4a, 146) In animal experiments, vascular and parenchymal lesions which could lead to hemorrhage or tissue injury have been found in the brain in vitamin K deficiency Whether tissue lesions precede hemorrhage in infants deficient in vitamin K is unknown It is of interest, however, that not a single instance of cerebral hemorrhage was noted in 1531 children in Oslo who were born of women who received vitamin K during the last weeks of pregnancy (159)

Vitamin K Deficiency

The outstanding manifestation of vitamin K deficiency is hemorrhage which may occur into any tissue or from any mucous membrane Cerebral hemorrhage is frequent in infants deficient in vitamin K and has also occurred in adults Diagnosis of vitamin K deficiency is dependent on estimation of prothrombin activity of blood A number of procedures are available for this purpose all of which consist of indirect estimation of prothrombin concentration (160)

Prothrombin time may be prolonged in conditions not

associated with vitamin K deficiency A number of anticoagulants which are used in the control of thrombosis and large doses of salicylates decrease prothrombin activity In severe liver disease, the formation of prothrombin is defective but administration of vitamin K is not beneficial

NUTRITIONAL DIAGNOSIS, THE FUTURE

From the foregoing discussion, it is obvious that much has been learned about the intricacies of nutritional problems and that numerous methods have been developed that are useful in delineating metabolic abnormalities and nutritional status It is of interest to speculate concerning *the future of the science* of nutrition as it may be applicable to diagnostic and therapeutic medicine Certainly much more information will be forthcoming about interrelationships and balance among nutrients Knowledge of nutritional aberrations in diseases not due primarily to nutritional fault is indeed meagre and should receive increasing attention The rapid strides made in biophysics and biochemistry in recent years will undoubtedly provide techniques which will be valuable in elucidating metabolic abnormalities Many of the disturbances which are uncovered may be amenable to nutritional therapy

One promising approach in nutritional diagnosis appears to be measurement of enzyme concentrations in tissue specimens obtained by biopsy Another is the possibility of testing nutritional adequacy by stressing various enzyme systems which may be found to be sensitive to the supply of a given nutrient and measuring metabolic end products Isotopic techniques should assist in discovering specific roles of nutrients in normal bodily function and in clarifying dysfunction that occurs in disease They may prove increasingly useful in diagnosis as well

While scientific advances may make many of the pro

cedures described in this monograph obsolete in the not too distant future, the approach to nutritional diagnosis will continue to be astute clinical evaluation of all facets of the patient and his problems Data obtained from the dietary, environmental and medical histories, from physical examination and laboratory procedures must be combined into an integrated whole for accurate diagnosis The physician must be well versed in basic knowledge of nutrition and keep abreast of advances in this field

Nutritional diagnosis is, or should be, an integral part of all medical diagnosis It is unfortunate that until recently nutritional aspects of medical problems have often received scant and superficial attention If this monograph stimulates an awareness of the potentialities of nutritional diagnosis and resultant therapeutic implications, it will have accomplished its primary purpose

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